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Original Communications

CLINICAL OBSERVATIONS UPON SYNCOPE AND SUDDEN DEATH IN RELATION TO AORTIC STENOSIS*

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and

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Although sudden and unexpected death is regarded by many laymen as the usual conclusion of all forms of heart disease, it is actually of such infrequent occurrence as to be the distinct exception, rather than the rule. There are but few cardiac conditions which terminate with dramatic abruptness sufficiently often to make one aware of such a probability. It is widely recognized that thrombotic closure of a coronary artery is not infrequently followed by sudden death, sometimes when the patient appears to be convalescing satisfactorily, and the occasional almost instantaneous deaths of patients suffering from anginal heart failure are too well known to require comment. It has long been a matter of medical knowledge that a small proportion of patients with complete A-V heart-block die with extreme suddenness, and this type of death is thought by many to occur frequently as a result of syphilitic aortitis with aortic insufficiency. In these four distinct manifestations of cardiac disease the prognosis is properly regarded as ominous, and most physicians are aware that a patient exhibiting any one of them may die suddenly at any time.

Apparently it is not widely recognized that there is another group of cardiac patients in whom the same hazard exists, namely, that composed of patients who have stenosis of the aortic orifice. A perusal of current textbooks upon diseases of the heart reveals a singular silence in this connection; in one of them[1] there is found the suggestive comment: "Sudden death (in cases of aortic stenosis) is not very uncommon"; and Cabot[2] in his admirable study of post-mortem records emphasizes the fact that in six of the twenty-eight cases of aortic stenosis "death was

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notably sudden and unexpected, though no explanation was found for this postmortem. In one case the patient died in the hospital corridor. As a rule the death was preceded by the usual symptoms of passive congestion and stasis.''

The occurrence, in the practice of one of us, of sudden unexpected death in two cases of aortic stenosis within one week led us to a systematic search of the medical literature of the past century in an effort to learn something of the apparent frequency of this association. We have found a number of casual comments upon the possibility of sudden death, or unsupported statements to the effect that death may occur suddenly, but apparently there has been no survey of this particular aspect of cardiovascular disease. A small number of case reports have been found, but the details are usually insufficient to warrant any conclusions. More than two centuries ago, Boneti[3] stated that Rayger had reported in 1672 the case of a patient who had died suddenly, and autopsy disclosed calcification of the three aortic cusps, which were ''so hard that only with difficulty could a portion be cut off with a knife.'' In 1846, Lloyd[4] reported sudden death in a man of fifty-two years; autopsy revealed immense hypertrophy of the heart and extreme narrowing of the aortic orifice, so that a probe could scarcely be passed through it. Gautier[5] in 1860 reported that death occurred with extreme suddenness in a boy of twenty years whose heart post mortem showed aortic stenosis and normal mitral valves. In 1868, Peacock[6] reported in greater detail the case of a patient twenty-three years of age who had suffered from slight palpitation and dyspnea for seven months. Six days before death he had substernal discomfort, vomiting, and exhaustion. On the day of death his feet began to swell. Examination on that day revealed signs of aortic stenosis and insufficiency, and that evening he was found dead on the floor of the toilet, where he had fallen from the seat, and had apparently died instantly. Autopsy showed the aortic valves fused in a funnel-shaped aperture so small as to admit only the extreme tip of the little finger. The heart was two and a half times the normal weight. Budin and Decaudin[7] gave a brief report of sudden death in a woman of forty-eight who was walking around her bed in the hospital. She had presented clinical signs of aortic stenosis and insufficiency; autopsy showed aortic stenosis with thickening and fusion of the valve cusps, which were infiltrated with calcium salts.

It was not, however, until 1875 that any general connection between aortic stenosis and sudden death was mentioned. In that year, Wilks and Moxon[8] made the following interesting comment:

''In very old diseased valves, calcareous changes may take place. . . . This petrifaction is the most frequent cause of simple aortic obstruction. The earthy concretions grow into great masses that invade the valves until at last they are converted into immovable nodular masses of stone, with the orifice of the aorta reduced to a little chink of the size and shape of the mouth of the uterus. Such examples

you may sometimes meet *as causes of the sudden death of hale-looking old men who never had dropsy,* and sometimes they are found in the bodies of old men who have died of independent diseases, even when the obstruction of the aorta is nearly absolute; such cases are very surprising, and prove how comparatively innocent is simple obstruction of the orifices.''

In recent years a few more instances of sudden death have been reported briefly. In 1921, Lutembacher[9] cited an instance in which autopsy revealed not only aortic stenosis of rheumatic type, but also blocking of the narrowed orifice by a large blood clot. Six years later Willins[10] reported the results of a follow-up study of ninety-six cases of aortic stenosis. Only seventy-six of these were successfully traced; of this number, fifty-six had died of cardiac disease in an average time of seventeen months after examination. In eight of these fifty-six, death had occurred suddenly. More recently Margolis, Ziellessen, and Barnes[11] studied forty-two cases of calcareous aortic valvular disease, the diagnosis being based entirely upon post-mortem examination. These authors state that sudden death occurred in five cases. ''In three of these cases considerable sclerosis of the coronary arteries was found, without evidence of occlusion, however; in one case there was severe cardiac decompensation. The fifth case in which sudden death occurred was that of a woman, suffering from exophthalmic goiter associated with auricular fibrillation and congestive cardiac failure. At necropsy the coronary arteries were found not to be sclerosed but there was stenosis of the aortic valve due to fusion and calcification of the right and left anterior cusps.'' It is impossible to determine from their paper how great was the degree of stenosis of the valve orifice in these cases, but it was probably very slight since a clinical diagnosis of aortic stenosis was made in only two of the forty-two patients. They state specifically that occlusion of any of the larger branches of the coronary vessels was not found in any case. It is important to note that their five patients who died suddenly were in their usual health; the authors state that ''a certain proportion of the patients died suddenly, although until the time of death they appeared to be *in normal health.*'' Christian[12] has recently reported twenty-one cases of aortic stenosis of the calcareous type, but there was no instance of sudden death in his series. Four of the patients reported by Campbell and Shackle[13] died ''absolutely suddenly without preliminary failure.'' It is not stated in their paper whether these four were in the atheromatous or syphilitic group, but Dr. Campbell has been kind enough to write us that three of them had atheromatous aortic stenosis, and one had syphilitic aortic insufficiency. The most comprehensive study to date is that of McGinn and White[14] who have quite recently reported upon 236 cases of aortic stenosis. Nine of the 172 deaths in this group were sudden; presumably six of these nine are those reported by Cabot,[2] since the same autopsy reports were used for both studies.

We have been able to find only one detailed report of syncope associated with aortic stenosis, although several references to the "syncope of aortic valve disease" have been encountered. Smith[15] has placed on record the report of a man thirty-six years of age who had seven or eight fainting spells in 1926, then four years of freedom, and a return of the fainting spells in 1930. The first of these occurred only with strenuous exertion, but by July, 1930, they came if he walked one block at a slightly faster rate than usual; the last one was induced by the effort of lifting his small son. Unconsciousness lasted from one-half minute to two minutes; he was pale, and cyanosis had not been noted; convulsive movements and twitching had never been observed. This patient exhibited the typical signs of aortic stenosis. The author states that "in cases of aortic stenosis with syncopal attacks, the same condition, that of cerebral anemia, probably exists, due to two principal factors: (1) the high degree of narrowing of the aortic orifice, and (2) fatigue of the left ventricle. Under conditions of stress, cerebral anemia results from the inability of the left ventricle to force blood through the narrowed orifice in sufficient amounts for the brain to function efficiently." Campbell and Shackle[16] report that syncopal attacks occurred in three of their patients with rheumatic aortic stenosis; two of them were in good health, but, in the third, anginal attacks had been followed by loss of consciousness on three or four occasions, and he died in one such attack. Four of their subjects with aortic stenosis of atheromatous or unknown origin were subject to syncopal attacks, and one of these died suddenly. The authors state that the cause of death in this last case was probably a Stokes-Adams attack, but in view of the following discussion we venture to think this improbable. Of the 236 patients with aortic stenosis reported by McGinn and White,[14] syncope occurred in 31; the authors do not discuss its cause or significance.

The infrequency of reports in the medical literature of the past eighty-five years, and the failure of practically all textbooks to mention either sudden death or syncope in connection with aortic stenosis, would lead to the impression that these occur only rarely. It is our belief that both syncope and sudden death occur with sufficient frequency to justify their association with this particular cardiac lesion, and the following report of eleven cases seems justified on the basis of its possible importance for prognosis and in order to stimulate interest in further study.

Of these patients, six were in the New Haven Hospital or Dispensary, and five were seen in private practice.

CASE REPORTS

CASE 1.—H. P. F., a white American housewife of forty-five years, had been conscious of dyspnea on exertion for several years, but had been troubled especially during the preceding six months. The effort of climbing one flight of stairs caused

considerable distress. Occasionally she awoke at night with a sense of substernal oppression and difficulty in breathing. Fatigue had been present most of the time. She had not suffered from cough, orthopnea, or edema.

She had had scarlet fever at the age of six years, and rheumatic fever at twelve years, with involvement of practically all joints. One year previously she had had severe tonsillitis, followed by another bout of rheumatic fever with multiple joint involvement. Tonsillectomy was performed shortly afterward.

Physical examination: She looked perfectly healthy. There was no cyanosis or dyspnea while at rest, and she was able to lie on one pillow without discomfort. There was no engorgement of the cervical veins. The apex impulse of the heart was visible and palpable in the fifth left intercostal space, 10 cm. from the median line. There was a short presystolic thrill at the apex and a coarse systolic thrill over the aortic area. The cardiac rhythm was regular, the rate normal. At the apex the first heart sound was moderately accentuated; it was preceded by a rumbling diastolic murmur and followed by a blowing systolic murmur. In the aortic area there was a very harsh, rough systolic murmur, well heard over the carotid and subclavian arteries; a prolonged diastolic murmur was audible beneath the upper sternum. The lungs were clear. The liver was not enlarged and there was no edema.

Electrocardiogram showed intraventricular heart-block. The blood Wassermann reaction was negative.

The diagnosis was thought to be rheumatic heart disease with stenosis and insufficiency of the mitral and aortic valves, and intraventricular heart-block.

For the next three years her cardiac condition remained practically unchanged. She continued to suffer from moderate limitation of physical exertion; one year later she thought this limitation was greater than before. The small remaining portions of tonsillar tissue were removed because of frequent sore throats and slight rheumatic pains. So far as can be learned, her last visit to a physician was six months prior to her death, when she was suffering from an acute infection of the upper respiratory tract. During the three years that elapsed between her first visit and her death, there was no apparent change in the physical signs over the heart or in the character of the murmurs. At no time did she develop signs of congestive heart failure.

One day when apparently as well as usual, she walked a short distance to visit a neighbor. On her return she paused in her own garden to pluck a flower, and fell dead.

Case 2.—J. C. M., a white American male of thirty-seven years, had complained of excessive gas in the stomach and shortness of breath for about eight years. Ten years earlier he had been refused admission to the U. S. Army because he was said to have heart disease with mitral insufficiency; at that time he had no symptoms. About two years later he began to have slight gaseous distension after meals, and dyspnea was first noted when exertion coincided with the presence of gas. Both symptoms had become gradually but steadily worse, until they interfered greatly with his physical activity. He had never suffered from orthopnea, cough on reclining, or edema of the lower extremities. His occupation involved relatively little physical activity.

There was no history of rheumatic fever, chorea, scarlet fever, or diphtheria. Severe tonsillitis had occurred several times.

Physical examination showed a well-developed, poorly nourished man without cyanosis, dyspnea, or engorgement of the cervical veins. In the erect posture, the apex impulse of the heart was visible and palpable in the seventh left intercostal space in the anterior axillary line; with the patient recumbent, it was maximal in the sixth intercostal space just beyond the mammary line. There was a sustained systolic thrill over the aortic area, felt also in the arteries of the neck. No thrill was felt at the apex. The rhythm was fundamentally regular, but was interrupted frequently by premature beats. There was a harsh, prolonged systolic murmur and a softer

blowing diastolic murmur in the aortic area and beneath the sternum; the systolic murmur was transmitted upward, the diastolic downward. Both heart sounds were absent in the aortic area. There was a softer systolic murmur over the lower precordium, but no diastolic murmur was heard. The position of the apex impulse shifted considerably with the rotation of the patient's body, and Broadbent's sign could not be demonstrated. Blood pressure was 120-125 mm. Hg systolic, 58-64 mm. diastolic. The lungs were clear to percussion and auscultation. The liver and spleen were not palpable. There was no edema of the lower extremities or lower back.

Electrocardiogram showed frequent auricular and junctional premature beats.

A seven-foot roentgenogram of the heart showed the transverse diameter of the thorax to be 29.5 cm. and that of the heart to be 16.4 cm. The enlargement of the heart was chiefly of the left ventricle. The aorta was normal in size.

The blood Wassermann reaction was negative.

The diagnosis was thought to be rheumatic heart disease with aortic stenosis and insufficiency and mitral insufficiency. There were no clear signs of mitral stenosis.

The patient was observed at regular intervals for the next eleven months. So long as he was careful about physical activity he was perfectly comfortable, and was gradually able to increase the amount of walking and light work about his store. He slept well on one pillow and did not have edema. Approximately one year after he first came under observation he went fishing, and while standing quietly on the bank of a brook, he suddenly fell to the ground and was dead when his companion reached him within a very few seconds.

CASE 3.—J. C., a white American male of forty-one years, complained chiefly of breathlessness. In November, 1929, while doing fairly heavy work, he experienced very severe pain beneath the sternum, radiating to both arms. This pain lasted at its maximal intensity for about a half hour, and then gradually subsided. He stopped work for the day, and on the following day seemed almost as well as usual; within a short time, however, he began to have typical anginal pain beneath the sternum, radiating down both arms; nitroglycerin afforded immediate relief. For a number of months the pain occurred almost exclusively at night, and often came several times. About four or five months later, he began to have paroxysmal nocturnal dyspnea, and this continued for several months, becoming gradually worse. By May, 1930, he was forced to sit in a chair all night in order to breathe. He was unable to carry on any significant physical activity, but was not confined to bed. He grew gradually worse until September, 1930, when he was admitted to a hospital. Anginal pain had then been absent for five months.

He had had severe rheumatic fever at the age of seventeen years.

Physical examination showed a large, well-developed man, propped up in bed and exhibiting marked dyspnea and orthopnea. There was moderate pallor of the skin and mucous membranes. There was no cyanosis and little or no venous engorgement in the neck. The apex impulse of the heart was considerably beyond the mammary line, almost in the anterior axillary line, in the fifth and possibly the sixth left intercostal spaces. There was a rather harsh systolic thrill in the aortic area; no thrill was felt with certainty at the apex. The cardiac rhythm was regular, the rate normal. Systolic and diastolic murmurs were audible over the entire precordium; in the aortic area the murmurs were typical of those associated with aortic stenosis and insufficiency. The aortic second sound was absent. A mitral diastolic murmur was thought to be present, but this was not certain. Blood pressure was 122/76. The lungs showed dullness and crackling râles over both bases posteriorly. The liver edge was palpable just below the right costal margin. There was slight edema of the right foot; none of the left.

A seven-foot roentgenogram of the heart showed the total transverse diameter to be 19.5 cm., and that of the thorax 31.5 cm. There was no widening of the aortic

shadow. Electrocardiograms on two occasions showed intraventricular heart-block of slight degree, the ventricular deflections being upward in Lead I and downward in Lead III.

The blood Wassermann reaction was negative.

The signs were thought to indicate rheumatic heart disease with stenosis and insufficiency of the aortic and mitral valves; anginal heart failure due to interference with the coronary circulation, probably by distortion of the orifices of the coronary arteries; congestive heart failure.

Four days later, when the nurse entered his room in the morning, he told her he felt very well and had had an excellent night's rest. She washed his face and hands and left the room for a period of about five minutes. When she returned she found him in the same position, dead. Autopsy was not permitted.

Case 4.—J. D., a white American male forty years of age, was admitted to the New Haven Hospital because of breathlessness on exertion; this had begun about two years previously and had slowly increased in severity. About two weeks before admission, following a severe cold with cough, he became rapidly worse, and developed orthopnea and edema of the lower extremities. The symptoms increased so steadily that his physician recommended hospital care. There was no history of rheumatic fever.

Physical examination: The patient was a well-developed, fairly well-nourished white man who exhibited marked dyspnea, orthopnea, and cyanosis. There was profuse sweating and frequent slight productive cough. The apex impulse of the heart was visible and palpable in the fifth and sixth left intercostal spaces in the anterior axillary line. There was a distinct systolic thrill in the aortic area, felt best with the patient sitting. No thrill was felt at the apex. Over the aortic area there was a very harsh, coarse systolic murmur, well heard over the carotid and subclavian arteries. The aortic second sound was absent. A soft diastolic murmur was audible beneath the sternum. A systolic murmur was audible at the apex, but no presystolic or diastolic murmur could be heard in this location. The cardiac rhythm was regular, the rate 90 per minute. The blood pressure was 110/62. The lungs showed numerous crackling râles over both bases. The liver extended about 4 cm. below the right costal margin. There was marked pitting edema of the lower extremities. There was no clubbing of the fingers or toes.

A seven-foot roentgenogram of the heart revealed considerable enlargement, chiefly of the left ventricle. The electrocardiogram showed normal mechanism.

Kahn and Wassermann tests upon the blood serum were negative.

The diagnosis was thought to be rheumatic heart disease with aortic stenosis and insufficiency, and congestive heart failure.

The patient improved and was discharged three weeks after admission, in fairly good condition. He went home and rested for two weeks, then returned to work in a wire factory. He continued working for two weeks, but noticed a return of edema in the lower extremities, dyspnea, orthopnea, and cough. Because of an increase in the severity of these symptoms he was taken to a hospital, where he remained for five weeks. He was discharged, again comparatively free of symptoms, and went home for three weeks. During this period, the dyspnea and orthopnea returned, and he spent much of the time in bed. Symptoms were induced by the slightest exertion, and he would awaken several times at night with a sense of suffocation, relieved by sitting up. He was again admitted to the New Haven Hospital.

During the fifty-seven days that he remained in this hospital he was propped up in bed or in a chair constantly. Digitalis was continued in maintenance doses, and he received various diuretics at frequent intervals. Despite these measures he became slowly but steadily worse. During the last two weeks of life, his condition changed very little from day to day. One morning he was sitting quietly in bed

while the nurse washed his hands. He suddenly became intensely cyanotic, and respirations ceased within a few seconds. Death occurred in about a minute.

Autopsy was performed the same day. The weight of the heart was 900 grams; the wall of the right ventricle measured 6 to 7 mm. in thickness, that of the left 18 mm. The pulmonary and tricuspid valves appeared normal in all respects. The mitral valve leaflets were thin, flexible, and normal in appearance, except for a few small, discrete, firm, translucent nodules along the free edges. These nodules measured 2 to 3 mm. in diameter, and felt like deposits of calcium within the valves. There was no stenosis of the mitral orifice. The aortic orifice, as seen from above, appeared to be a tiny slit; it measured only 6 to 7 mm. in its greatest diameter, and was so distorted that the original boundaries of the individual valve cusps could not be determined; they remained only as greatly thickened, fused, calcified structures. On the aortic surface of the anterior cusp, there was a small friable ante-mortem thrombus. The orifices of the coronary arteries were patent, and careful dissection of all the major branches failed to reveal any occlusion. Microscopically, the only significant change consisted in enormous hypertrophy of the muscle fibers. No increase in connective tissue was seen.

Case 5.—F. R., a Jewish woman of twenty-nine years, stated that she had suffered from dyspnea on exertion for about ten years. This symptom was said not to have increased in severity during the past two or three years. She had never had orthopnea, cough on reclining, pain over the liver, or edema. She had suffered from severe rheumatic fever in early adult life.

At the time of her first visit to the New Haven Dispensary, physical examination revealed slight cyanosis of the lips. There was no venous engorgement in the neck, and no dyspnea while at rest. The apex impulse of the heart was visible and palpable in the fifth left intercostal space in the anterior axillary line. A presystolic thrill was palpable over the apical thrust and a coarse, prolonged systolic thrill in the second right intercostal space near the sternum. The cardiac rhythm was regular and the rate normal. At the apex the first heart sound was greatly accentuated and continued into a blowing systolic murmur; the second sound was followed by a low-pitched murmur that extended through most of diastole. In the aortic area there was a loud, harsh systolic murmur transmitted to the arteries in the neck; a prolonged diastolic murmur was audible beneath the upper sternum and along the left sternal border. The position of the apex impulse shifted several centimeters with rotation of the patient's body. The blood pressure was 144/86. There were no signs of visceral congestion and no edema. The blood Wassermann reaction was negative.

The physical signs were regarded as those of rheumatic heart disease with stenosis and insufficiency of the mitral and aortic valves.

Five and a half years later she was admitted to the New Haven Hospital because of slowly increasing congestive heart failure. For some months she had suffered from dyspnea, orthopnea, and physical weakness. The heart was found to have increased greatly in size during the intervening years; the apex impulse was in the sixth left intercostal space beyond the anterior axillary line. The rhythm was totally irregular, the rate normal. The heart sounds and murmurs were as described above. The blood pressure was 140-146 mm. Hg systolic, 80-90 mm. diastolic. The liver was slightly enlarged but not tender. There was no edema.

Fluoroscopic examination confirmed the clinical finding of great cardiac enlargement, and revealed conspicuous dilatation of both auricles. Electrocardiogram showed auricular fibrillation and digitalis depression of the S-T intervals in Leads I and II; there was no axis deviation. The urine contained a faint trace of albumin, but was otherwise normal. The Kahn reaction on the blood serum was negative. Other laboratory examinations revealed nothing of significance.

She remained in the hospital for twenty-five days, most of the time at complete rest in bed. Digitalis was continued in doses sufficient to control the cardiac rate; other treatment was purely symptomatic. There was steady improvement, and she left the hospital feeling quite comfortable. About one week later she suddenly fell dead in her home. Autopsy was not performed.

CASE 6.—J. L., a Jewish man of fifty-eight years, was admitted to the New Haven Hospital because of symptoms of heart failure. He had noticed moderate breathlessness on exertion for several years, but it had not interfered seriously with his activity until several months before. Two weeks prior to his admission, he stopped work in order to rest for a week, but his improvement was not great, and on the morning of admission he found he was unable to walk even the short distance to a trolley line.

A review of his past and family histories revealed no items of importance.

Physical examination: The patient was rather emaciated. There was considerable dyspnea while at complete rest, greatly increased by slight exertion. There was slight cyanosis of the lips; no venous engorgement in the neck. The apex impulse of the heart was visible and palpable in the fifth and sixth left intercostal spaces beyond the mammary line. There was a short thrill over the apex, thought to be presystolic in time, and a coarse sustained systolic thrill over the aortic area. The cardiac rhythm was regular, the rate normal. In the aortic area there was a loud, rough systolic murmur transmitted to the arteries of the neck. The aortic second sound was absent. There was a prolonged diastolic murmur beneath the sternum. At the apex there were systolic and diastolic murmurs, different in quality from those at the base. Blood pressure was 138/70. The lungs showed dullness and numerous crackling râles over the lower portions. The liver edge was just above the level of the umbilicus. There was no edema. The Wassermann reaction on the blood serum was negative.

The physical signs were interpreted as indicating rheumatic heart disease with stenosis and insufficiency of the aortic and mitral valves, and congestive heart failure.

He was admitted to the hospital about 7 P.M. and received morphine hypodermically at once. He vomited small amounts of fluid at 10 P.M. and at 3:30 A.M. He was not regarded as critically ill; his condition was such that it was believed he would improve with rest and medication. He seemed to be quite comfortable until 4:50 A.M., when there was sudden extreme respiratory distress and he was dead within several minutes.

Autopsy: The heart weighed 750 grams. There was marked sclerosis of the coronary arteries, but no obstruction could be found in any of them. The three cusps of the aortic valve were very rigid, brittle, and fused together into a calcified mass which projected into the aorta like a crater. The orifice at its widest diameter measured 1 cm.; it was completely occluded by a blood clot which was firmly adherent to the free edges of the valve. At the point of adhesion, the thrombus was pale and friable; in the center it was dark red and elastic. The orifices of the coronary arteries were not obstructed. The cavity of the left ventricle was relatively enormous. The wall of the right ventricle was 6 mm. in thickness, that of the left was 18 mm. The mitral orifice was considerably narrowed by fusion of the valve edges. The leaflets were thickened, especially at the free edges and were less freely movable than normal. At the point of fusion of the two valves anteriorly, the endocardium was replaced by a rough calcareous area. The chordae tendineae were thickened. The pulmonary and tricuspid valves were normal in size and appearance. Microscopic examination revealed a great increase in size of the muscle fibers of the left ventricle. Scattered throughout the walls of this chamber were small collections of mononuclear leucocytes; these were located chiefly about the arterioles, but some of them were seen transecting groups of muscle fibers. Some sections of the left ventricle showed great increase in connective tissue.

It is interesting to know that six years earlier this patient had reported at the New Haven Dispensary because of pain in the left wrist, present for two days. The following note was made at that time by the interne:

"The heart shows a systolic thrill over the aortic area and a very loud systolic murmur over the greater part of the upper right chest and along the arteries of the neck; it is loudest over the aortic area. There are systolic and diastolic murmurs at the apex. Pulse is of the plateau type. Blood pressure 140/100. Impression: Aortic stenosis and insufficiency."

Case 7.—K. J., an American housewife of forty years, was first seen in the New Haven Dispensary in February, 1923. At that time she stated that she had suddenly lost consciousness four times in the preceding two years, and on many occasions had felt faint without actually losing consciousness. She remained unconscious for from three to thirty minutes, and on one occasion she is said to have been cyanotic. All four episodes immediately followed excitement or unusual exertion. She had no aura but usually had a sense of oppression beneath the upper sternum just before fainting. She had never injured herself, there had been no twitching of the limbs or the head, no convulsions, and no urinary or fecal incontinence. The pulse rate was counted once while she was unconscious and was said to have been between 60 and 70 per minute. She had not suffered from unusual dyspnea, cough, orthopnea, palpitation, or edema.

The past history was not recorded. At the age of nineteen years she had been told that she had heart disease.

Physical examination showed a pale, undernourished woman, quite tall but weighing only 110 pounds. There was no dyspnea, orthopnea, cyanosis, or engorgement of the cervical veins. The apex impulse of the heart was visible in the sixth left intercostal space in the anterior axillary line. There was a prolonged systolic thrill over the aortic area; no thrill was felt at the apex. The cardiac rhythm was regular and the rate normal. Over the apex the first heart sound was very loud and banging, and continued into a loud systolic murmur; no diastolic murmur could be heard. In the aortic area there was an intense coarse systolic murmur, audible also over the carotid and subclavian arteries. The aortic second sound was extremely faint, and there was a prolonged blowing diastolic murmur along the left sternal border. The position of the apical thrust shifted readily with rotation of the patient's body. The blood pressure was 100/72. The lungs were clear. The liver was not enlarged. There was no edema.

The Wassermann reaction on the blood serum was negative.

The signs were interpreted as indicating rheumatic heart disease with aortic stenosis and insufficiency, mitral insufficiency and possibly mitral stenosis.

One year later she reported that she had not had any fainting spells, but had occasionally noticed pronounced dizziness on walking. While at rest, she felt entirely comfortable. Two months later she lost consciousness while walking along the street and remained unconscious for at least fifteen minutes before she was found. Aside from slight bruises there was no injury. Three weeks later, just after eating dinner, she again lost consciousness. At this time she stated that there had been a sense of slight oppression beneath the upper sternum just before she fainted.

One year later her physician was called to see her because the fainting spells were occurring more frequently. X-ray films of the teeth were secured and showed numerous apical abscesses. All the teeth were removed and three weeks later the physician was informed by the patient's husband that she felt much better. About two weeks afterward she was sitting quietly conversing with her husband, when she suddenly fell from her chair and was dead by the time he could reach her side.

Autopsy was not permitted.

CASE 8.—S. N., a Jewish farmer of fifty-two years, was sent to the New Haven Hospital by his physician for observation and rest. He stated that two years earlier he had suddenly fallen unconscious while running in pursuit of his cattle. He did not know how long he remained unconscious, but was later able to walk slowly to his home, feeling as if he were intoxicated. About one month later he again fainted while running, and was just recovering consciousness two hours later when found by his wife. Within six months he had experienced eight similar episodes, all of them occurring while he was running or doing heavy manual labor on his farm. Upon the advice of his physician, he stopped farm work for five months; he then resumed his work, but noticed great difficulty in walking, especially up hills or up stairs. After walking for only one or two minutes, he had a sensation of oppression beneath the sternum, and increasing dizziness; everything would begin to turn black, and he felt that he would lose consciousness if he did not sit down or lean against a support. For the nine months preceding his admission to the hospital, he had worked very little. He had not suffered from orthopnea, cough, or edema.

His past health had been excellent; he could recall no illnesses.

Physical examination: The patient was well developed and nourished and did not exhibit cyanosis, dyspnea, or venous engorgement while at rest. The apex impulse of the heart was palpable in the fifth left intercostal space beyond the mammary line. There was a distinct systolic thrill in the aortic area, felt best during expiration with the patient leaning forward. No thrill was felt at the apex. The cardiac rhythm was regular, the rate normal. The heart sounds were of poor quality. In the aortic area and over the carotid and subclavian arteries there was a loud, harsh systolic murmur. The aortic second sound was absent. No diastolic murmur was heard over any portion of the precordium. The blood pressure was 120/80. There was moderate sclerosis of the peripheral arteries. There were no signs of visceral engorgement.

A seven-foot roentgenogram of the heart revealed moderate enlargement of the left ventricle. There was no dilatation of either auricle, and the aorta was normal in size and shape. Electrocardiogram showed normal sinus mechanism. The blood Wassermann was repeatedly negative.

The signs were interpreted as indicating aortic stenosis without insufficiency; the etiology was thought to be uncertain.

He remained in the hospital for one month, the only treatment being rest. On several occasions while walking about his room he was forced to stop because of increasing dizziness; he felt sure that he would lose consciousness if he continued the exertion.

He was readmitted to the hospital six months later because of signs and symptoms of congestive heart failure. These had appeared several weeks previously, following an infection of the upper respiratory tract. At this time he displayed the classical signs of heart failure with venous congestion. The physical signs relating to the heart were unchanged except for increased rate. There was moderate improvement as a result of rest and the administration of digitalis, and he was discharged after three weeks, to continue resting at home.

Ten weeks later he was admitted for the third time because of rapidly increasing heart failure. He remained in the hospital for three months; at first there was some response to digitalis and diuretics, but later he became steadily worse, and died. Death did not occur suddenly.

Post-mortem examination: The heart weighed 750 grams. There was an increase in the thickness of the left ventricular wall. The mitral, pulmonary, and tricuspid valves appeared perfectly normal. The aortic orifice, as viewed from above, was narrowed to a minute slitlike opening which would barely admit a small probe; when opened, the aortic orifice measured only 5 cm. in circumference. The valves were greatly distorted, thickened, and calcified. In the sinuses of Valsalva there were

large calcified masses, extending to the valve cusps. The right anterior and posterior cusps were completely fused by calcareous masses. On the margins of all three cusps there were a few very small friable granulations. Microscopic examination revealed a notable increase in the size of muscle fibers of the left ventricle. Throughout the walls of this chamber there was fine diffuse fibrosis in addition to large islands of denser scarring. The orifices of the coronary arteries were patent, and no obstruction could be found in any of their branches.

CASE 9.—F. B. F., a white American housewife of sixty-two years, complained of pain in the left shoulder and down the outer aspect of the left arm as far as the wrist. This was said to have been present for at least twenty years, and was elicited only by physical exertion. For the preceding two years, pain had occurred also over the precordium, often beginning in the left breast and radiating to the shoulder and down the outer aspect of the arm. It had never been experienced beneath the sternum, had never been constricting or tearing in character, never severe enough to make her cease walking, and had invariably disappeared within five or ten minutes, although she continued walking. Six months earlier, she had suddenly fainted while walking along the street. She was unconscious for only about a minute, and upon recovering consciousness felt perfectly well. She consulted a physician who told her she had heart disease; this was her first knowledge that anything was wrong with her heart. She had never suffered from dyspnea, orthopnea, cough, or edema.

Careful questioning about the past history and family history revealed no items of significance.

Physical examination: The patient looked perfectly healthy; her color was excellent; the respirations were entirely normal during rest and quiet activity. There was no venous engorgement in the neck. The size of the heart could not be satisfactorily determined by physical examination; the apex impulse was faintly felt in the fifth and possibly the sixth left intercostal spaces just outside the mid-clavicular line. There was a systolic thrill over the aortic area, also felt over the subclavian arteries; no thrill was felt at the apex. The cardiac rhythm was regular, the rate 80 per minute. In the aortic area there was a harsh, prolonged systolic murmur, transmitted to the carotid and subclavian arteries. The aortic second sound was absent. In a very small area at the left sternal border at the level of the third costal cartilage, a soft short diastolic murmur could be heard. There was a short blowing systolic murmur at the apex. The blood pressure was 184/96. There was moderate arteriosclerosis of the radial, brachial, and retinal arteries. The lungs were normal to percussion and auscultation. The liver was slightly enlarged. There was no edema.

Fluoroscopic examination revealed moderate enlargement of the heart, the increase in size apparently involving only the left ventricle. There was no dilatation of either auricle, and the aorta was of normal size. Electrocardiogram showed normal sinus mechanism, left axis deviation, and slight inversion of the T-waves in Leads I and II. Tho Wassermann reaction on the blood serum was negative.

The physical signs were interpreted as indicating aortic stenosis and very slight insufficiency; the etiology was thought to be arteriosclerosis, possibly subsequent to rheumatic damage.

During the following year there were repeated episodes characterized by sudden loss of consciousness. These usually lasted about ten minutes and invariably occurred during, or immediately at the conclusion of, such physical exertion as walking along the level or up one flight of stairs. These continued until her physical exertion was practically ended by the onset of congestive heart failure, of which she died two and one-half years after her first visit. Death was not sudden or unexpected. Autopsy was not performed.

CASE 10.—H. H., a white American woman of fifty-eight years, was referred for examination because of fainting spells. Twice within two months she had suddenly lost consciousness while walking along the street: she was unconscious for ten minutes on the first occasion, and about three minutes on the second. For about a year she had noticed slight breathlessness after climbing hills or stairs, but none while walking along the level. She had never had orthopnea, cough, edema, or substernal pain.

She had never had rheumatic fever, chorea, scarlet fever, or diphtheria. There had been frequent tonsillitis in earlier life.

Physical examination: She appeared perfectly healthy. Color and respirations were normal. The apex impulse of the heart could not be seen or felt. There was a distinct systolic thrill in the aortic area; none was felt elsewhere. The cardiac rhythm was regular and the rate normal. In the aortic area there was a very loud, rasping systolic murmur well transmitted to the arteries in the neck. The aortic second sound was extremely faint. There was a very faint short diastolic murmur beneath the upper sternum, audible only when the patient stopped breathing. The blood pressure was 162/96. There was slight sclerosis of the retinal arteries and moderate sclerosis of the radial and brachial arteries.

Fluoroscopic examination revealed moderate enlargement of the left ventricle and increased density of the aortic shadow. There was no dilatation of the auricles. The aorta was normal in size. The electrocardiogram showed left axis deviation; the conduction intervals and ventricular deflections were normal.

The Wassermann reaction on the blood serum was negative.

The physical signs were regarded as those of aortic stenosis with slight insufficiency. It was thought that the lesion was probably arteriosclerotic but possibly rheumatic, or a combination of the two.

For several months she was free from syncope, then for many weeks noted dizziness on walking; this would disappear upon cessation of the exertion. After a few months, however, she began to have complete loss of consciousness associated with walking or with other forms of physical exercise. About eighteen months after her visit she became unwilling to go out of doors because the effort of walking even very short distances often caused syncope, which lasted from three to ten or fifteen minutes. On several occasions she fell unconscious on the street even though for several preceding days she had been able to walk without difficulty. She did not develop congestive heart failure. Almost exactly two years after she came under observation, she walked upstairs to get her hat, preparatory to starting on a motor ride. Her husband and sister heard her fall to the floor, and rushed at once to her; she was completely unconscious, and died within several minutes.

CASE 11.—A white, married, American salesman sixty years of age was admitted to the New Haven Hospital in May, 1930, because of dizziness, palpitation, and dyspnea. He had suddenly become dizzy and lost consciousness for the first time nine months previously, and had then felt perfectly well until one month before admission. At that time he had a typical paroxysm of nocturnal cardiac dyspnea, relieved promptly by the administration of morphine.

The past and family histories disclosed no items of apparent importance.

Physical examination showed obesity, moderate dyspnea and orthopnea, slight engorgement of lungs and liver. The heart was not enlarged as judged by physical examination, there was gallop rhythm and a faint systolic murmur at the apex. There was no note of a basal systolic murmur. The blood pressure was 100 to 130 systolic, 60 to 70 diastolic. The prostate gland was enlarged. There was no edema. Examinations of the blood, urine, and stools yielded normal findings; the chemical components of the blood and the renal function tests were likewise normal. Electrocardiograms on several occasions showed moderate physiological tachycardia, left axis deviation, and occasional ventricular premature beats. The Kahn test on the blood serum was negative.

The clinical diagnosis was arteriosclerotic heart disease with early congestive heart failure. Treatment consisted of rest in bed, limitation of fluids, and the administration of sedatives and of digitalis; after two weeks he was perfectly comfortable and was discharged.

He reported at intervals of one to three months at the Cardiac Clinic of the New Haven Dispensary from June, 1930, until October, 1932; it was not until this latter date that he first came to the attention of one of us. He stated that during the two and a half years since his discharge from the hospital, he had not suffered from the symptoms of congestive or anginal heart failure, but that his entire difficulty had consisted of loss of consciousness associated with walking. A review of his written records showed that he had fainted sixteen times during that period, always during or immediately at the cessation of walking. At times he could walk four or five blocks before losing consciousness; at other times, he would faint after walking less than a half block. The time of day, the season, the temperature and humidity, the presence of food in the stomach, his feeling of well-being or the reverse, all appeared to be without effect; he stated that he could induce fainting at any time by walking a short distance. His first abnormal sensation was one of great emptiness in the upper abdomen and lower chest; this extended rapidly upward to the neck, he became dizzy and lost consciousness within a few seconds of the first warning. The period of total unconsciousness lasted from five to fifteen or twenty minutes as a rule; this was followed by one or two hours of weakness, after which there was complete recovery. So long as he refrained from walking he felt perfectly well, and could perform his regular duties as a hardware salesman.

Examination at this time disclosed no findings of interest other than those relating to the heart. The heart's apex lay in the fifth left intercostal space, directly in the mammillary line. No thrill could be felt with certainty at the apex or base. The rhythm was regular, the rate normal. In the aortic area there was a harsh but not very intense systolic murmur, typical in all respects of that usually associated with aortic stenosis, and well heard over the subclavian and carotid arteries. The aortic second sound was absent. No diastolic murmur could be heard by any of several examiners. The blood pressure was 150/98. There were no signs of venous congestion. It was our impression that the patient had aortic stenosis of the calcareous type, without signs of aortic insufficiency, and that the syncope was in some way related to the narrowing of the aortic orifice.

Treatment was purely symptomatic; at various times he took digitalis, metaphyllin and quinidine, but without clear evidence of benefit. He continued to have occasional syncope, always during or immediately after walking, with a single exception. On that one occasion he was sitting quietly in a chair, and leaned forward to place a small box over a plant. As he sat up again, he realized that he was about to faint, but was able to walk about fifteen feet to a couch, and fell unconscious upon it. Following this episode, however, he could sometimes walk for an hour twice a day for some weeks without losing consciousness, only to faint unexpectedly after walking less than a hundred yards. Altogether, he had about thirty episodes during the period from October, 1930, until May, 1933.

During part of this time, we had tried vainly to persuade him to precipitate an attack in the cardiographic laboratory by means of deliberate exercise, but he was afraid that each episode might prove fatal, and was unwilling to provoke one voluntarily. However, in May, 1933, he consented to permit observations, of which an abbreviated protocol follows:

Unfortunately, the following observations are incomplete and unsatisfactory for several reasons: The room was in semidarkness most of the time in order to secure electrocardiograms, and the noise of his stertorous respirations and the convulsive

movements of the arms made it difficult to secure satisfactory curves and to hear the heart sounds. A preliminary electrocardiogram of the usual three leads was secured. The time is recorded in minutes.

0 Preliminary electrocardiogram completed (Fig. 1*A*).

1¾ The patient started walking from the laboratory into the adjacent room, a total distance of about 20 feet. He swung his arms vigorously all the time in order to increase the exertion.

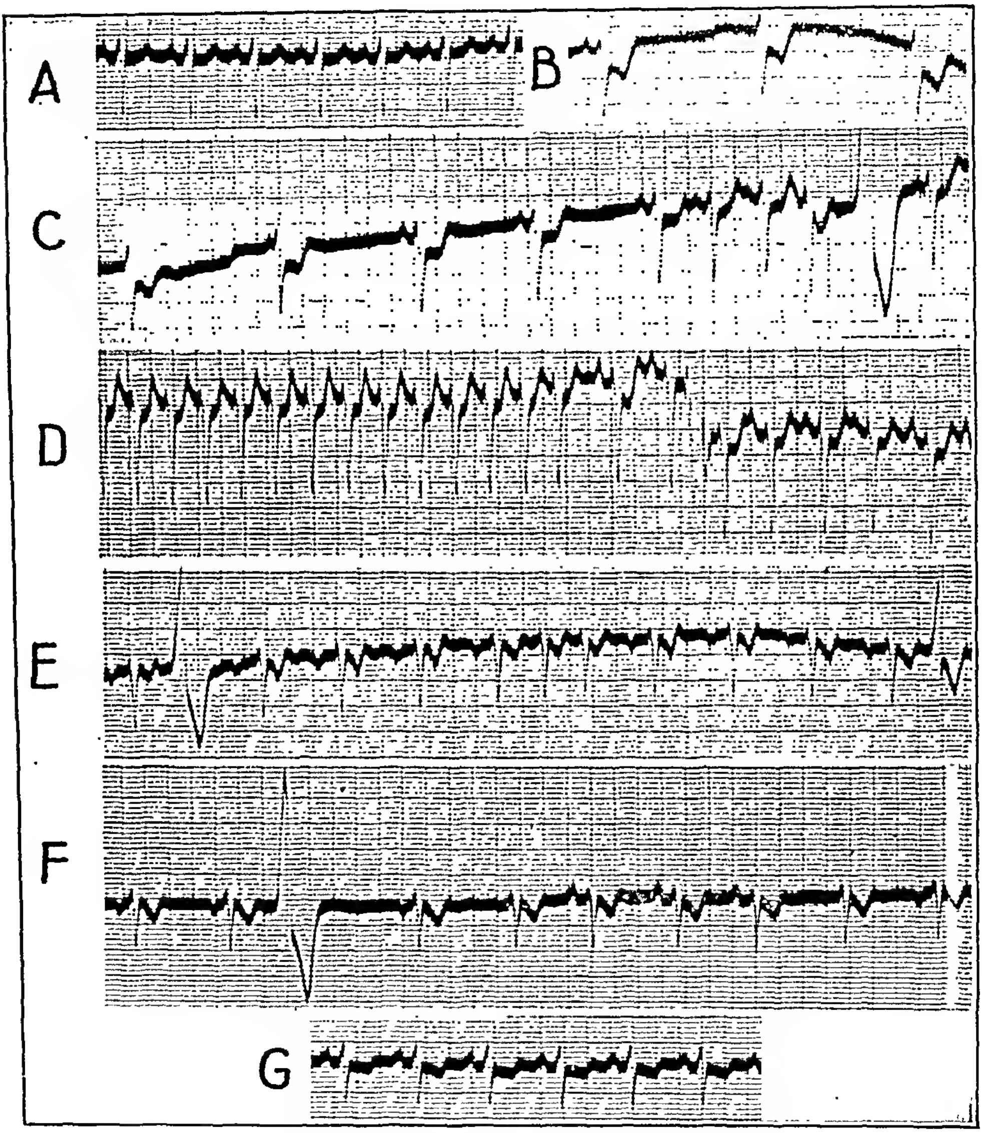

Fig. 1.—Electrocardiograms of Case 11. All records are of Lead II. Time is in fifths of a second.

A, Before exercise.

B, Just after onset of syncope. Nodal rhythm, bradycardia, and marked depression of origin of T-wave.

C, A few seconds after *B*; patient completely unconscious. Return of sinus mechanism and appearance of ventricular premature beats.

D, A half minute after *C*. Paroxysmal tachycardia, rate 200 per minute.

E, About three minutes after *D*; patient conscious. Auricular and ventricular premature beats and inversion of T-wave.

F, Ninety seconds after *E*; patient fully conscious. Shifting pacemaker. Ventricular premature beats.

G, Four minutes after *F*. Premature beats have ceased. T-wave is apparently returning toward normal.

For more complete description see the text.

5 At the end of the seventh trip (a total distance of approximately 280 feet) his color was grayish white, and he sat on the edge of the couch, stating that he was fairly certain he was about to lose consciousness. Unfortunately, an electrocardiogram was not secured at this moment; it was delayed in the belief that further exercise might be necessary. Within a few seconds, however, he lay down on the couch, his eyes rolled upward, the breathing became stertorous and quite loud. As soon as possible an electrocardiogram was secured; it began at the sixth minute. The record was terminated in the middle of Lead II by convulsive movements of the patient's arm which made it impossible to keep the string shadow focused on the camera. The rate in the earlier portion of the record was approximately 70 per minute and irregular; in the latter portion it was about 50 per minute and regular. Lead I showed ventricular escape and nodal rhythm, but the ventricular deflections were unaltered. Lead II showed a continuation of nodal rhythm and a profound change in the T-wave which had its origin below the zero level and turned sharply downward (Fig. 1*B*). The blood pressure during the period of slow rate was 124/80. After a few seconds of waiting, another portion of Lead II was secured which showed the return of normal mechanism, then a sudden increase in rate and the appearance of ventricular premature beats (Fig. 1*C*). There was now complete loss of consciousness with deep, noisy respirations, occasional movements of the right arm and head, and slighter, less frequent movements of both legs.

8 This record (Fig. 1*D*) was started at the eighth minute, about thirty seconds after the conclusion of the preceding curve. It showed simple paroxysmal tachycardia with a rate of 200 per minute; there was a change to sino-auricular tachycardia about the middle of the record. At this moment the patient began to sigh and muttered a few words, but it was clear that he had not fully recovered consciousness. Blood pressure had risen to 190/100.

11 The patient seemed to be fully conscious but continued to sigh loudly and to roll his head impatiently from side to side. The rate of the heart was slightly above normal, and there were occasional premature beats. Electrocardiogram showed inversion of the auricular waves and continued inversion of the T-wave which did not, however, arise so far below the base line. There were premature beats arising in both auricles and ventricles (Fig. 1*E*).

12½ Patient more quiet. Premature beats less frequent. Blood pressure 160/90. Electrocardiogram (Lead II) shows P- and T-waves still inverted. (Fig. 1*F*).

14 Cardiac rate and rhythm normal. Blood pressure 156/90.

16½ Electrocardiogram (Lead II) shows normal mechanism with slight depression of the S-T interval and T-wave (Fig. 1*G*).

17 All three leads of electrocardiogram taken. In comparison with those obtained before exercise, there were a few minor changes. The ventricular deflections were smaller in all three leads of the second record; the T-wave in Lead I was more deeply inverted than in the preexercise curves; and in Lead II the S-T interval was depressed in the second record, although the T-wave in this lead was upright in the first.

18 Cardiac rhythm regular. Blood pressure 126/90.

23 The patient said he felt very warm, but was perspiring less than usual after recovering consciousness. He thought this episode was typical in all respects but less severe than most, which he ascribed to the fact that he was able to lie down as soon as he felt any discomfort.

30 He felt just as usual after an attack. (He remained at rest for another hour and then was taken to his home by automobile.)

Comment.—It seems clear that electrocardiograms should have been taken as soon as the patient felt uneasy rather than after the loss of consciousness. Auscultation of the heart was practically valueless for a time because of the noisy respirations and the patient's groaning. The electrocardiograms revealed several changes that are possibly of importance:

(1) A considerable reduction in the rate of the heart.
(2) The onset of A-V nodal rhythm.
(3) A remarkable change in the T-wave in Lead II, which arose from the ascending limb of the S-wave considerably below the zero line.
(4) Occurrence of many ectopic beats, shortly followed by simple paroxysmal tachycardia at a rate of 200 per minute.
(5) Conspicuous and deep inversion of the T-wave in Lead II, different from that mentioned in (3), which gradually became less and in the final curves was manifested as moderate depression of the S-T interval.
(6) Frequent changes in position of the pacemaker after the subsidence of the tachycardia.

Repeated attempts were made to induce this patient to return for a repetition of the entire procedure, but he refused. Some months after these observations had been made there appeared the splendid paper by Weiss and Baker,[21] which first made us suspect the possibility of hyperactivity of the carotid sinus in this and similar cases.

From May until November, 1933, the patient had only three or four syncopal attacks, and on most days was able to walk for at least two hours without symptoms. On November 8, he felt as well as usual, and was walking about in his yard, but in the late afternoon he came indoors, telling his wife that he was about to faint. He was able to reach his bed before losing consciousness, and the attack seemed to his wife exactly similar to all previous ones. After about ten minutes he had recovered sufficiently to smile and speak to her; within several minutes, however, another similar episode began and progressed to its usual conclusion. Once more he smiled at her as he regained consciousness, but almost immediately a third syncopal attack began, and he died within five minutes, just as his physician reached the room. His wife and daughter, who had witnessed most of his attacks, were emphatic in stating that the three of this day were precisely similar in appearance to all the earlier ones; the changes in color and in breathing, the convulsive movements, the duration, the slow recovery were just as they had been on previous occasions.

Autopsy was performed at the New Haven Hospital about four hours later. The heart was moderately enlarged, its weight being 483 grams. There was extreme stenosis of the aortic orifice with dense calcification of all cusps which were converted into a single firm mass. The orifice was reduced to a narrow slit about 2 mm. wide and 6 mm. to 7 mm. long. There was moderate hypertrophy of the left ventricle, with but little dilatation. The mitral, tricuspid, and pulmonary valves were normal in appearance. The orifices of the coronary arteries were patent, and no evidence of occlusion could be found in any branch. Microscopically the heart showed hypertrophy of the muscle fibers with very little fibrosis. Both carotid sinuses were removed, and no abnormality could be detected grossly or microscopically.

DISCUSSION

Of these eleven cases, it seems reasonably certain that the first seven had the rheumatic type of heart disease; in the remaining four cases, the etiology must be regarded as less certain. These four presumably

Table I

CASE	SEX	AGE	TYPE OF HEART DISEASE	AORTIC INSUFFICIENCY	MITRAL STENOSIS	CONGESTIVE HEART FAILURE	SYNCOPE	INDUCED BY	DURATION	TYPE OF DEATH	REMARKS
1	F	45	Rheumatic	+	+	0	0			Sudden	Intraventricular heart-block.
2	M	37	Rheumatic	+	+	Dyspnea only	0			Sudden	
3	M	41	Rheumatic	+	+	Advanced	0			Sudden	Anginal failure some months earlier. Intraventricular heart-block (slight).
4	M	40	Rheumatic	+	0	Advanced	0			Sudden	Autopsy performed.
5	F	35	Rheumatic	+	+	Slight	0			Sudden	
6	M	58	Rheumatic	+	+	Moderate	0			Sudden	Closure of aortic orifice by thrombus (autopsy).
7	F	30	Rheumatic	+	?	0	Many	Exertion or eating	3 to 30 minutes	Sudden	
8	M	53	?	?	0	None at time of syncope	Many	Exertion	Minutes or hours	Progressive heart failure	Autopsy performed.
9	F	62	Rheumatic Arterio-clerotic	Slight	0	0	Many	Exertion	10 minutes	Progressive heart failure	
10	F	58	?	Slight	0	0	Many	Exertion	3 to 10 minutes	Sudden	
11	M	60	?	0	0	0	Many	Exertion	5 to 20 minutes	Sudden	Autopsy performed.

belong in the group that has been discussed at some length by numerous observers[2, 11, 12, 14, 17, 18]—the group composed of elderly people who present clinical signs of aortic stenosis with or without slight aortic insufficiency and who, at post-mortem examination, show moderate or extreme calcification of the aortic valve cusps and no disease of the mitral valves. After a consideration of all the known factors relating to etiology, most of the above authors have reached the conclusion that the cardiac lesions are probably rheumatic in type, with subsequent arteriosclerotic changes, but recognize that the question of etiology has not been answered with entire satisfaction. In the present paper we refer to this type of aortic stenosis as arteriosclerotic or calcareous for the sake of uniformity and brevity, but it is our belief that the etiology is yet uncertain. Of our first seven cases, six patients were forty-five years of age or less, and all presented unequivocal clinical signs of rheumatic heart disease. Even if the remaining four cases be regarded as also primarily rheumatic, it is quite possible that the signs and symptoms were not due to the original lesions, but rather to calcareous changes that occurred only after the passage of many years. The point might seem of purely academic interest were it not for a possible difference in the symptomatology of the two groups. In the cases here reported, for instance, sudden death occurred in all of the seven rheumatic patients and syncope in but one of them. Campbell and Shackle[16] also found a higher incidence of syncope in the cases of atheromatous aortic stenosis than in those of rheumatic type.

A brief summary of the significant facts relating to these eleven patients is contained in Table I. It will be observed that nine died with extreme suddenness, and four of these had no heart failure at the time; another (Case 2) had no symptoms except slight dyspnea on exertion, and was apparently better than he had been for many months. The remaining four (Cases 3 to 6) had slight or advanced congestive heart failure but were no worse on the day of death than they had been for days or weeks; in fact, one of them was apparently improving steadily. Autopsy in three cases failed to reveal any adequate cause for the sudden death; in one the cause was thought to be complete thrombotic closure of the narrowed aortic orifice. In five of the eleven patients, repeated fainting spells constituted the chief symptom; in all of these, syncope occurred chiefly or only in association with physical exertion. It has already been mentioned that four of these five had the calcareous type of aortic stenosis. One of them lived for approximately two years after the onset of syncope, two for about three years, and one for six years. Three of these five died suddenly, one of the rheumatic and two of the arteriosclerotic group.

Such, briefly, are the known facts relating to these patients. The problems which they present are the two indicated in the title of the paper: why are they subject to sudden prolonged loss of consciousness while

carrying on slight physical exertion, and why do many of them die with extreme suddenness when apparently quite well? It is perhaps impossible, on the basis of the imperfect and inadequate evidence now available, to arrive at an acceptable answer, but the possibilities may be indicated briefly. Those relating to the suddenness of death will be considered first.

Sudden Death.—Embolic closure of a large artery (coronary, pulmonary, or cerebral) is one of the first possibilities that comes to mind in cases of sudden death, but there are many reasons for believing it inacceptable as an explanation in the patients now under consideration In most of these, auricular fibrillation is not present, and aortic stenosis in itself does not provide any unusual opportunity for the formation of intracardiac thrombi. Moreover, death caused by large emboli is seldom as instantaneous as that in the patients here presented; almost invariably it is delayed for at least several minutes after the occurrence of the vascular accident, and in many instances the patients give some indication of the location of greatest distress by clutching at the chest, gasping for breath, etc. Apparently the patients who have aortic stenosis die in seconds rather than minutes, and the abruptness of the termination strongly resembles that sometimes observed in anginal patients or in those who have recently sustained myocardial infarction. A final, and in itself conclusive, argument against the acceptance of the embolic theory is found in the fact that post-mortem examination has not revealed such an embolus in any reported case, and it is impossible to believe that one large enough to cause immediate death could be invariably overlooked by pathologists.

Sudden occlusion of the small aortic orifice by a blood clot formed in situ is a possibility that would seem incredibly remote had it not been demonstrated in one case previously reported[9] and in Case 6 of the present group. It would seem almost impossible that a blood clot could form in an orifice constantly exposed to the full force of left ventricular contraction, and it is probable that in both of the known cases there was extreme weakness of the left ventricle at the time the thrombus formed. There is of course the possibility that in both the clot was a post-mortem one and had no causal relation to the sudden death. Even if one accepts these two as conclusive, however, it remains true that the great majority of recorded cases have failed to show thrombotic closure of the aortic orifice, and this must be regarded as a rare event.

Interference with the coronary circulation by distortion of the orifices of these arteries, with subsequent thrombotic closure of a large branch, might explain the suddenness of death in some instances, but in most it cannot be regarded as the explanation because careful search post mortem in a number of cases has failed to reveal any such lesion. Moreover, increasing experience with patients who have suffered coronary arterial thrombosis indicates that death from this cause is seldom in-

stantaneous at the time of the initial closure; it is far more liable to occur after a few minutes, several hours, or several days.

That abrupt death cannot be satisfactorily explained on the basis of mechanical narrowing of the aortic orifice is sufficiently indicated by two considerations. It has long been known that patients with extreme stenosis of this orifice may live for months or years in comparative comfort and even carry on fairly strenuous physical activity; this is a matter that has received widespread comment. Moreover, many patients with aortic stenosis have died not abruptly, but in the usual slowly progressive fashion characteristic of congestive heart failure, even though the aortic opening was much smaller than in others who died suddenly. If the mechanical narrowing were important, one would expect a certain parallelism between extreme degrees of stenosis and the tendency to die suddenly. In some of the cases reported by Margolis and his associates the degree of stenosis was so slight that it was not recognized clinically, yet death occurred with extreme suddenness.

It is possible that the size of the heart may be of some importance in determining whether or not sudden death will occur. It is certainly true that in the group here reported enlargement of the heart was much greater in those patients who died suddenly than in the others. If one adopts the view that death in such cases is due to the onset of ventricular fibrillation, there are observations suggesting that this is more liable to occur in large hearts than in small ones.[19, 20] Whether or not this suggestion applies to the cases reported by Cabot, Margolis, and Willius cannot be known because the degree of enlargement of the heart is not stated by these authors.

There is as yet no clear proof that the cause of death in these patients is the same as that of syncope; it is at least conceivable that they are due to entirely separate and unrelated causes, and do not represent simply major and minor reactions to the same stimulus. It is natural and proper, however, to assume for the moment that syncope and sudden death may owe their origin to the same mechanism, and the events in our Cases 7, 10, and 11 would appear to lend strong support to this view, for in all of them death occurred suddenly after a long series of syncopal attacks, and one of these patients died during a seizure which seemed typical of all its predecessors. The evidence afforded by this one case is actually of the greatest value, for the circumstances of the last few moments of life are known accurately, and he had been the subject of careful preceding observations. To state that death occurred in one instance during, or at the termination of, a typical syncope is to imply that a common cause might have been responsible for both loss of consciousness and cessation of life.

This implication leads directly to the consideration of hyperactivity of the carotid sinus reflex as a cause of death—a possibility that was un-

recognized by us during the study of our first ten cases. The fainting in many of these patients is apparently quite similar to that attributed by numerous observers to this reflex, and the whole series of antemortem observations in Case 11 can be duplicated in several of the cases reported in the admirable and careful study of Weiss and Baker.[21] There is, however, one major difficulty in accepting hyperactivity of this reflex as the cause, namely, that death has not occurred suddenly in any reported patients known to have hyperactivity of this reflex. Weiss[22] states that none of the patients observed by him have died in a manner that could be attributed to the carotid sinus mechanism, and that the spontaneous syncope in their patients was of brief duration.

We are not prepared as yet to acknowledge that this difficulty is sufficient to exclude the carotid sinus reflex as a cause of death, for on theoretical grounds it would seem highly probable that death might result from a mechanism capable of causing profound vasomotor changes and extensive alterations in the cardiac mechanism. Further observations alone can solve the problem, but in the present state of our knowledge it seems well to suggest that death in the present group of cases might have been due to hyperactivity of the carotid sinus reflex in patients who had aortic stenosis also.

From this brief consideration it seems reasonably clear that the cause of sudden death in a great majority of these patients is not to be found in embolism, thrombosis, or mechanical narrowing of the aortic orifice. It is our belief that the cause is probably either (a) the combination of aortic stenosis and hyperactive carotid sinus reflex, or (b) the same mechanism that terminates life in many patients who have anginal heart failure or who have sustained recent thrombosis of a coronary artery. It seems to be the prevailing opinion that this mechanism is dependent upon the onset of ventricular fibrillation or upon a depressor reflex other than that involving the carotid sinus, but conclusive evidence of its precise nature is yet to be obtained.

It will be observed that six of our first seven patients had mitral stenosis in addition to aortic stenosis and insufficiency, and the question naturally arises as to its possible relation to the sudden death. That this lesion is almost certainly unimportant in the group of cases now under discussion is indicated by two facts: (1) In cases of mitral stenosis and insufficiency without evidence of aortic valve damage, sudden death during the maintenance of regular cardiac rhythm is exceedingly rare. When auricular fibrillation has been added, unexpected and fairly rapid death occurs not infrequently as a result of cerebral or pulmonary embolism. In a fairly extensive experience with cases of mitral stenosis, we have never known an example of the type of death discussed in this paper. Cabot[2] lists two patients of his 107 cases of mitral stenosis as having died suddenly, but the details of these cases show that one patient lived for five days after the onset of unexplained coma, and the other

lived for some hours after becoming unconscious; this is not the type of "sudden" death with which we are here concerned. (2) The majority of recorded cases of sudden death have been in patients who did not have mitral stenosis as shown by autopsy; this was true of all those reported by Cabot and by Margolis, and of three cases (Nos. 4, 6, and 11) of the present group.

A more important question, and one that will inevitably be asked, is why we are warranted in assuming that the sudden death in these patients is related to the aortic stenosis rather than to the aortic insufficiency. It is difficult to answer this with convincing certainty, but there are several reasons which appear to indicate that it is the obstruction rather than the regurgitation which is the important factor. It is realized that many observers during the past century have referred to the suddenness of death sometimes associated with aortic insufficiency or, more frequently, with the indefinite lesion designated "aortic valve disease." It is often impossible, in the case of the earlier writers, to ascertain whether the lesion in their cases was stenosis or insufficiency or both. Even when it is clear that aortic insufficiency was present without stenosis, it is probable that in many instances the etiology was syphilis. In the absence of more precise studies and more detailed descriptions, one cannot be unduly influenced by general statements without known foundation; we have been unable to find any satisfactory evidence to warrant the belief that nonsyphilitic aortic insufficiency without stenosis is a cause of sudden death or frequent syncope. It is our belief that sudden death of patients with aortic insufficiency without stenosis occurs with extreme rarity except in one clearly defined pathological state, namely, syphilitic aortic insufficiency. That it does occur at times in this condition is undoubtedly true, but its frequency has possibly been exaggerated. It is pertinent to indicate in this connection that no patient of the present group had any evidence of syphilis; that is true also of the cases reported by Cabot, by Margolis and his collaborators, and presumably, though not certainly, true of the cases reported by Willius. Three patients of the four cases of sudden death reported by Campbell and Shackle[13] did not have syphilis.

If one considers examples of acquired aortic insufficiency due to all causes other than syphilis, it is more difficult to make a positive statement. It seems probable that there are but two other groups; the rheumatic group, in which the aortic lesion is almost always associated with mitral stenosis, and the arteriosclerotic-hypertensive group. The rheumatic group is discussed later in some detail and need not be mentioned further at this point. The other group is far smaller and less well defined; its existence is actually denied by some competent observers, but there can be no question that a small proportion of middle-aged or elderly people who have arteriosclerosis with or without hypertension, do present clinically an unmistakable diastolic murmur at the base of the heart and

beneath the sternum. Very often the usual peripheral vascular signs associated with aortic regurgitation are absent, but sometimes these too are present. Signs of mitral stenosis are entirely lacking.* The group is too small to be of importance, and we have no figures comparable with those given below. Of the last 123 patients dying in this hospital as a result of the arteriosclerotic type of heart disease, only five had physical signs of aortic insufficiency during life. None of these died suddenly.

The fact that those who have reported previous cases have emphasized the stenosis rather than the insufficiency as the cause of sudden death is probably quite without importance, because the diagnosis in their cases was based on autopsy findings; the anatomical lesion in such patients is stenosis, and the presence of regurgitation during life is deduced, not demonstrated. Both Cabot and Margolis state that insufficiency *must* have been present in their cases; the absence of physical signs of this condition during life is a point of no value whatever in view of the fact that signs of aortic stenosis were not found during life in many of Cabot's cases, and were described in only two of Margolis' cases. Granting that their patients had clear post-mortem evidence of stenosis and insufficiency, it becomes impossible to assert, on the basis of these cases alone, that death was due to one rather than to the other. Evidence must be sought in analogous cases, and this is attempted briefly in the paragraphs that follow.

Conclusive observations bearing upon this point could be obtained readily if there were comparable groups of patients having "pure" aortic insufficiency and "pure" aortic stenosis. The first group is available in those who have syphilitic involvement of the aortic valves, but the second is so small as to be negligible, because almost all patients with aortic stenosis have insufficiency also. It has therefore seemed to us that the most decisive evidence was to be derived from a comparison of two groups of patients, the first having mitral stenosis and aortic insufficiency, the second having these same lesions plus aortic stenosis. In such a comparison, we are dealing with two groups as nearly identical as possible with respect to age, sex, etiological factors and anatomical damage; the only important difference between them is the presence of aortic stenosis in one group and its absence from the other. If narrowing of the aortic orifice is actually the important lesion in relation to sudden death, there should be a notable difference in the two series.†

*We do not wish to be understood as expressing the opinion that aortic insufficiency in these patients is due to arteriosclerosis. We regard the etiology as uncertain, realizing that it may be rheumatic.

†We are in agreement with Cabot that rheumatism tends to cause stenosis (as well as insufficiency) in the case of both mitral and aortic valves, and recognize that it is merely a later stage of a single disease process. And while it is clear that aortic stenosis is frequently overlooked during life, even by careful examiners, we are not wholly in agreement with his statement that physical signs of rheumatic aortic insufficiency justify the assumption that aortic stenosis is present also. His rule could doubtless be applied with greater accuracy to hospital patients with congestive heart failure than to the large group of living patients who have no symptoms referable to the heart. It seems clear that there must be a stage in the pathological process when insufficiency is present without demonstrable narrowing of the orifice.

We have therefore reviewed our records, both of hospital and of private cases, and have divided them into two such groups. We have been careful to exclude all cases of syphilitic heart disease, all cases of mitral stenosis without signs of aortic involvement, all cases of aortic lesions without signs of mitral involvement, and all cases among elderly people having arteriosclerosis and hypertension, in which the etiology of the heart disease might be questioned. During the period represented by the eleven cases here reported, we have observed a total of 108 cases in Group I (mitral stenosis and aortic insufficiency), and 64 cases in Group II (mitral and aortic stenosis and insufficiency). Of these, 30 patients are known to have died in Group I, and 36 in Group II. Not one of the deaths in Group I was of the sudden, unexpected type, while 9 in the other group were of this type (the nine cases reported in the present paper). One patient in Group I died quite rapidly, but this patient had subacute bacterial endocarditis and had suffered repeated embolic accidents; the clinical signs preceding death were those of cerebral embolism, and this diagnosis was confirmed by autopsy.

While the evidence with respect to this point cannot be regarded as absolutely conclusive on the basis of such a small number of cases, it seems nevertheless to lend strong support to the belief that aortic stenosis is the most important lesion predisposing to unexpected and practically instantaneous death. We have already indicated our agreement with the opinion that acquired aortic stenosis without insufficiency is a relatively rare condition, and the above statement should not be regarded as necessarily applying to this small group. It is perhaps clearer to say that in our opinion sudden death is unlikely to occur in cases of rheumatic heart disease without aortic stenosis, but is quite liable to occur in rheumatic heart disease with aortic stenosis, as well as in the older patients with aortic stenosis of the calcareous type.

Syncope.—The consideration of syncope and its probable cause in these patients is rather unsatisfactory. We have been unable to find any study of this symptom in relation to aortic stenosis, and but one detailed report of a case which falls clearly into the group now under discussion. In that case, reported by Smith,[15] the close and invariable association of transient syncope with physical exertion seems, at first glance, sufficient to warrant the explanation that he gives, namely, temporary cerebral anemia due to inability of the left ventricle to force sufficient blood through the narrow aortic orifice. In three of our five cases it is tempting to advance a similar reason, but there are several characteristics of the syncopal attacks that are not satisfactorily explained on this basis. In the first place, syncope occurred in four of our patients during quiet walking along a level street, and, what is particularly significant, occurred only infrequently. These patients could walk quite freely most of the time without any disturbance, but occasionally would lose consciousness without warning. In the second place, one of our patients

(Case 7) sometimes lost consciousness when she was standing or sitting; this occurred more often just after meals, but sometimes hours later. In the third place, it is difficult to understand why cerebral anemia dependent upon exertion should produce unconsciousness lasting for thirty minutes or even for several hours. In only one of our five cases (Case 8) was there any relationship between the severity of the physical exertion and the occurrence of syncope; in the other four, fainting was just as liable to occur after slight as after more strenuous exertion. It seems clear that exertion is an important factor in most cases, but it is far from certain that it is the only one.

That the loss of consciousness in these patients is due in all likelihood to cerebral anemia seems evident enough to require no extended argument; in none of them was there any suspicion of epilepsy; in none have generalized convulsions ever been observed. Transient complete heart-block, with Stokes-Adams attacks during the maintenance of the block, is clearly inadequate to explain the symptoms; the loss of consciousness is far longer than that in Stokes-Adams seizures; the electrocardiogram between syncopal attacks has shown normal mechanism in four of our five cases and in the one reported by Smith; and in at least two instances the heart rate has been counted while the patient was unconscious, and it was but moderately reduced.

Can the syncope be regarded as similar to that occurring in circumstances attended with considerable emotion—the fainting of people who witness gruesome accidents, who see the withdrawal of blood or surgical operations for the first time—the so-called vasovagal syncope? It seems highly doubtful, because the inciting cause in these patients appears to be physical exertion rather than an emotional influence, and because the duration of unconsciousness is far greater than in vasovagal syncope.*

Transient ventricular fibrillation as a cause of the fainting is rendered unlikely by several observations: the almost invariable association with effort, the long duration of unconsciousness, the absence of significant cardiac symptoms between the episodes of fainting, and the frequent repetition of syncope in some cases for long periods of time. Our present knowledge of ventricular fibrillation scarcely permits the assumption that it could manifest itself in this fashion repeatedly over a period of six years, as in our Case 7, or three and a half years as in Case 11.

Hyperactivity of the carotid sinus reflex, already discussed briefly as a possible cause of sudden death, would seem to be even more likely as a cause of the syncope. From a physiological standpoint the circumstances attending the loss of consciousness in the cases here reported are such as to justify the assumption that the sinus was stimulated by the rise of pressure in the carotid artery due to exertion. There is reason to believe that the effects of this normal stimulus would be similar in

*Lewis[23] suggests that the vasovagal seizures may be set up through the same central and efferent mechanism which takes part in the carotid sinus reflex.

type to those following artificial stimulation; these have been lucidly portrayed by Weiss and Baker[21] and need not be discussed at this point further than to indicate that faintness, dizziness, loss of consciousness, and convulsive movements are among the most constant symptoms resulting from direct artificial stimulation. The episodes of fainting in our patients appear to be similar to those reported as occurring after such stimulation of the carotid sinus in normal individuals, and the entire series of events in our Case 11 may be duplicated in several of those reported by Weiss and Baker.* There are, however, two obvious objections to immediate acceptance of hyperactivity of this reflex as the cause of fainting: one is that syncope due to deliberate stimulation of the sinus is usually of brief duration, whereas in several of our patients it lasted for a long time; the other is that the only instances of fainting of this type (occurring in association with moderate exertion, in the absence of such causes as organic disease of the central nervous system, epilepsy, anemia, marked hypotension, great physical weakness, emotional disturbances, etc.) observed by us in the past several years have been in patients with aortic stenosis. The second objection is probably more apparent than real, and further experience will doubtless remove it, although it is conceivable that stimulation of the carotid sinus reflex may occur more readily and lead to more profound and lasting effects in patients with aortic stenosis than in others. As to the first objection, we recognize that our statements about the duration of unconsciousness are open to question; we have relied upon the observations of relatives of the patients, and these may have been inaccurate. Of our five cases, the syncope was of relatively brief duration in three, and in the other two also most of the time, but in these two the unconsciousness is said to have lasted from thirty minutes to two hours on several occasions. However, even if this statement be accepted as accurate, it seems to us probable that the duration of unconsciousness might well be longer in patients whose aortic orifice is greatly reduced in size, for this would tend to lessen still further the cerebral blood supply, already reduced by vasoconstriction.

The evidence as a whole is not absolutely conclusive, but is such as to lead us to suggest that hyperactivity of the carotid sinus is the probable cause of the syncope in patients who have aortic stenosis. Direct stimulation of the carotid sinus in individuals similar to those recorded here will supply much evidence; it is unfortunate that this was not performed in our patients, but we were not familiar with the effects of this procedure in man until our last patient was under observation, and he refused to submit to it.

It is possibly worthy of note that of the five subjects who had syncope, only one presented the clinical signs of free aortic regurgitation.

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*It is not clear in their cases how close was the association between physical exertion and syncope: of the twelve cases of spontaneous fainting, exertion was apparently related in three, not related in three, and questionable in six.

examination failed to reveal an apparent cause for the sudden death in three cases; in one, the narrowed aortic aperture was completely closed by a thrombus thought to have formed during life.

Five of the eleven patients were subject to sudden and unexpected loss of consciousness associated with slight or strenuous physical exertion. In three of them the unconsciousness lasted from three to ten minutes; in the other two for much longer periods. Three of those subject to syncope died very suddenly and the others of progressive heart failure.

The possible causes of sudden death and of syncope, and their possible relationship to aortic stenosis, are discussed briefly. The present evidence does not justify final conclusions, but it is suggested that sudden death may be due to hyperactivity of the carotid sinus reflex associated with aortic stenosis, or to the same mechanism that terminates life in patients suffering from anginal heart failure or recent myocardial infarction. The relationship between aortic stenosis and syncope is not clear in most instances, but the available evidence does not support the belief that fainting is due to cerebral anemia dependent upon inability of the left ventricle to force sufficient blood through the stenotic orifice. It is far more probable that loss of consciousness is due, in many instances at least, to hyperactivity of the carotid sinus reflex or to a reflex involving the same central and efferent pathways. The widespread impression that syncope is often a symptom of aortic insufficiency we believe to be erroneous.

From the standpoint of prognosis it is of some importance to realize that patients with aortic stenosis may die unexpectedly and with extreme suddenness. How frequently sudden death occurs in those subject to syncope cannot be stated on the basis of the present small group.

SUPPLEMENTARY NOTE

After this paper was written, Dr. Maurice Campbell of London was kind enough to send us full details of several of his cases, and with his consent two of them are briefly summarized herewith.

CASE 1.—A man of forty-six years had been well until January, 1930, when he complained of having to sit down frequently because of dizziness at his work. He had sometimes fainted but had not suffered from dyspnea. There was no substernal discomfort or pain, but a sensation as if the chest were fixed in position.

He had had rheumatism for five weeks in childhood. In August, 1929, his chest was squeezed against a truck when a heavy sack of grain fell upon him; he thought his ribs were fractured, but x-ray examination was negative.

Physical examination in April, 1930, showed the apex impulse of the heart to be one inch outside the mammary line. There was a coarse systolic murmur and thrill in the aortic area, and the aortic second sound was inaudible. No diastolic murmur was heard. Blood pressure was 140/70. There were no signs of congestive heart failure. Kahn and Wassermann reactions were negative.

Despite the advice of his attending physician, he insisted upon doing heavy physical work, and on the day of his death was engaged in digging a drain. When

bicycling home from work in December, 1931, he died suddenly. An autopsy was performed in a neighboring house; the essential finding was extreme stenosis of the aortic orifice, which was almost totally closed. There was marked calcification of the cusps. There was a healed tuberculous nodule at the apex of the left lung and a cystic left kidney; otherwise there was nothing of interest. (The photographs sent by Dr. Campbell show that the aortic orifice was just large enough to admit a small probe.)

CASE 2.—A woman of forty-two years who was admitted to the hospital on June 20, 1934, complained of breathlessness, fatigue and loss of weight. She had been subject to syncopal attacks for three years, and syncope preceded the usual symptoms of congestive heart failure. Her past history disclosed no illnesses of importance other than scarlet fever at the age of seventeen years.

At the time of admission she presented the usual signs of advanced congestive heart failure, but without ascites or hydrothorax. The heart was enlarged and presented a systolic thrill in the aortic area, and systolic and diastolic murmurs. There was gallop rhythm at the apex. The systolic blood pressure was 105; the diastolic indeterminate. The electrocardiogram showed normal sinus mechanism with left axis deviation. Orthodiagram showed enlargement of the left ventricle; the transverse diameter of the heart was 14.5 cm. and that of the thorax 22 cm.

The patient responded splendidly to the administration of digitalis and salyrgan. Just as she was about to start getting up, she died very suddenly in syncope. Postmortem examination showed the aortic valve reduced to a very small slit. The cusps were calcified and absolutely rigid. The mitral and tricuspid valves were normal, as were the coronary arteries. There was great hypertrophy of the left ventricle.

Dr. Campbell adds the comment that death in this case was absolutely sudden and unexpected, and that he believes it to be not uncommon in this type of aortic stenosis.

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FURTHER EXPERIENCES WITH TOTAL THYROIDECTOMY IN THE TREATMENT OF INTRACTABLE HEART DISEASE*

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SINCE it was first suggested[1] that the removal of a normal thyroid gland might be helpful in the treatment of intractable chronic heart disease, a sufficient time has elapsed to permit of at least a preliminary review of its value. This present analysis will be confined to cases which were treated at the Peter Bent Brigham Hospital. The first twelve such cases were previously reported,[2] and some follow-up notes of these will be discussed below. The main purpose is to report thirty additional cases in which the normal thyroid gland was completely removed and to evaluate the results obtained.

REVIEW OF CASES PREVIOUSLY REPORTED

In the first two cases a subtotal thyroidectomy was performed. When it was found[3] in some cases that clinical improvement was temporary, it was thought that the remaining tissue had regenerated, and therefore complete removal of the gland was practiced thereafter. These first twelve patients were suffering from far advanced cardiac disease. It seemed only justifiable to try out a new procedure in hopeless cases when life was practically intolerable. The therapeutic results must be viewed with this in mind.

CASE 1. (Med. No. 37679.) Female, sixty-one years old. Diagnosis: hypertensive heart disease, auricular fibrillation and extreme congestive failure. Operation: subtotal thyroidectomy June 27, 1927, by Dr. F. C. Newton. Patient made an extraordinary and unexpected improvement, remained ambulatory and in good health and free from all congestion for about four years. She died with congestive heart failure on January 16, 1932.

CASE 2. (Med. No. 40940.) Male, fifty-three years old. Diagnosis: hypertension and angina pectoris. Subtotal thyroidectomy was performed on June 15, 1932, by Dr. John Homans. The anginal attacks were slightly improved. He died of angina pectoris on January 12, 1934. The result here was not satisfactory.

CASE 3. (Med. No. 42478.) Male, forty-three years old. Diagnosis: thromboangiitis obliterans, hypertension with both congestive failure and angina pectoris, cirrhosis of liver (?), thrombosis of portal vein (?). Total thyroidectomy was performed December 14, 1932.† The anginal attacks disappeared entirely for about six months and were only rare thereafter. Dyspnea and recurrent ascites developed, the

*From the Medical and Surgical Clinics of the Peter Bent Brigham Hospital, Boston, Mass.

†This and all subsequent operations were performed by Dr. E. C. Cutler, surgeon-in-chief of the Peter Bent Brigham Hospital.

entire course being rather atypical. He died on September 7, 1932. Post-mortem examination showed thrombosis with almost complete occlusion of the abdominal aorta and extreme sclerosis with tendency to occlusion of almost all the arteries of the body. No thyroid tissue remained. The result in this case was excellent for angina pectoris during the nine months of his life.

CASE 4. (Med. No. 39768.) Female, sixty-one years old. Diagnosis: hypertension, severe angina pectoris, moderate congestive heart failure, and previous coronary thrombosis. Operation February 4, 1933. There was complete relief of angina for five months when a second attack of coronary thrombosis occurred. Since then angina has recurred infrequently. The element of dyspnea is slightly ameliorated. Fifteen months after the operation the result can be considered satisfactory.

CASE 5. (Med. No. 41570.) Male, sixty-one years old. Diagnosis: chronic myocarditis, complete heart-block, auricular fibrillation and marked congestive failure. Operation March 9, 1933. Improvement was marked. Patient remained ambulatory and comfortable for four months. Ascites then developed and he died August 27, 1933. Post-mortem examination showed fibrous myocarditis and cirrhosis of the liver. The result here, though of short duration, was excellent, for a bedridden cardiac patient requiring frequent chest taps was made comfortable and ambulatory for some months.

CASE 6. (Med. No. 40453.) Female, forty years old. Diagnosis: mitral and aortic stenosis and insufficiency, auricular fibrillation, calcification of pericardium and marked congestive failure. Operation April 7, 1933. This patient's life, which had been quite miserable for a few years so that she was in hospitals practically all the time, was slightly improved. She is still alive thirteen months after operation but is invalided.

CASE 7. (Med. No. 42742.) Male, seventy years old. Diagnosis: coronary thrombosis (recent), marked congestive failure. Operation April 11, 1933, while he was practically moribund. Died the following day. Post-mortem examination showed occlusion of the left coronary artery and aneurysm of the left ventricle. It was an error to have operated on such a patient.

CASE 8. (Med. No. 42822.) Male, fifty-three years old. Diagnosis: mitral stenosis, auricular fibrillation, marked congestive heart failure. Operation May 19, 1933. There was slight apparent improvement for a few months. He gradually failed and died on October 8, 1933. Post-mortem examination showed calcified stenosis of mitral and aortic valves. Three small bits of thyroid tissue were found, weighing about one gram.

CASE 9. (Med. No. 43101.) Male, forty-five years old. Diagnosis: mitral stenosis, auricular fibrillation, cirrhosis of liver. Operation May 26, 1933. Improvement was only very slight. He died September 22, 1933, two days after an exploratory pericardiotomy. Post-mortem examination showed marked mitral stenosis and "Zuckergussleber."

CASE 10. (Med. No. 42229.) Female, twenty-nine years old. Diagnosis: mitral stenosis, auricular fibrillation, chronic nephritis and marked congestive heart failure. Operation June 5, 1933. Improvement was very slight. She required several hospital readmissions, although she was able to lie flat—which was impossible before operation. She died on March 21, 1934.

CASE 11. (Med. No. 43259.) Male, fifty-nine years old. Diagnosis: syphilitic aortitis, aortic insufficiency, angina pectoris and cardiac asthma. Operation July 7, 1933. There was complete freedom from anginal attacks which previously were frequent and most severe. He died at home in an attack of acute pulmonary edema on July 26, 1933, after a few days of nocturnal dyspnea.

CASE 12. (Med. No. 43307.) Colored male, forty-three years old. Diagnosis: hypertensive heart disease, auricular fibrillation with marked congestive failure. Operation August 3, 1933. Now, ten months after operation the patient is ambulatory and leading a life of moderate activity. The improvement here seems extraordinary considering the grave, refractory preoperative condition.

In judging the value of the results obtained in the first twelve cases and also in those to be reported below, there are various considerations that need to be taken into account. In the first place, one must ascertain whether improvement took place either in the elements that make up the picture of congestive heart failure or in the frequency and severity of the anginal attacks. These are the two purposes for which the operation is intended. A second question which arises is whether any significant harmful effects resulted from the operation. Finally one might rightfully ask whether improvement, if it occurs, is worth while. The severity of the diseases with which these patients were suffering is clearly indicated by the fact that six of the nine patients who survived total thyroidectomy died of heart disease within nine months. The first two patients with subtotal thyroidectomy survived four and one-half and one and one-half years respectively. There were three who are still alive, sixteen, fourteen, and ten months after total thyroidectomy. One of these three is bedridden; although her life is probably prolonged, her impoverished economic state has made the survival period a great burden to her and to those caring for her. The careful analysis of the preoperative and postoperative events shows that some improvement, though occasionally only slight, took place in all instances. The advanced stage of the underlying pathological processes did not permit most of these patients to enjoy the improvement for any great length of time. The fact that any improvement could occur and that a few were rendered ambulatory after having been bedridden previously gave us courage to continue this work. In the following cases, however, an attempt was made to select somewhat more hopeful patients.

SELECTION OF CASES

In the selection of cases there are a few fundamental principles which, in the present stage of this work, are directly applicable. No patient should be subjected to this operation who is able to carry on his occupation. Furthermore, if the patient is unable to work, but his financial status permits him to lead a life of leisure, provided he is comfortable, operation would not be advised. It is obvious that the economic and social status of the individual plays an important rôle in selection. If a man has angina pectoris and either gets adequate relief by taking nitroglycerin or is able to lead a life which avoids attacks, he would not be considered a suitable case. On the other hand, if the same man had to do some walking which was necessary in his

daily work and he was dependent upon this for a livelihood, operation would be recommended with the hope of economic rehabilitation. There is as yet no evidence to show that the operation prolongs the life of a patient with angina pectoris, and therefore it cannot be recommended with this in view. In fact, as will be seen later, subsequent coronary thrombosis has not been prevented by total thyroidectomy. It follows, therefore, that in a patient with angina pectoris the specific criteria to help in the selection of suitable cases are the frequency and severity of attacks and to what extent they are making life intolerable. So far, the level of the blood pressure, the history of previous coronary thromboses or the presence of abnormalities in the electrocardiograms have not been significant factors in our selection. If the attack of coronary thrombosis was very recent, a sufficient time should have elapsed to permit one to judge whether recurrent anginal attacks will be troublesome or not.

With regard to selection of cases with congestive heart failure, the problem is more difficult. There are some obvious contraindications to the operation, i.e., bacterial endocarditis or active rheumatic carditis. It is not known that infections of any sort would be materially helped by this procedure. A further contraindication is an accompanying renal insufficiency not dependent upon simple passive congestion of the kidneys. Likewise cirrhosis of the liver presents a real handicap. It may be difficult to ascertain whether an enlarged liver in the presence of congestion is irreparably cirrhotic or will recede with improvement in the circulation. The frequency of repeated abdominal tappings and the length of time which the liver has been known to be enlarged, help somewhat in differentiating the two conditions. Furthermore it might be inadvisable to select a patient who has some unrelated handicap like hemiplegia which would of itself greatly diminish the value of any improvement that the operation might produce. Finally, the ordinary life expectancy, the history or pattern of the particular cardiac disease needs careful consideration. It is well known that when significant congestive heart failure develops in patients with aortic stenosis or luetic aortic insufficiency the expected span of life is very short. Only a more extensive experience will tell whether such patients may be expected to receive consistent improvement by the operation. At present if such patients are selected at all, it should be done with no great optimism.

Mitral stenosis and hypertension associated with congestive failure are more liable to go through several cycles of relapses and remissions extending over a longer time and from this point of view are more suitable. Auricular fibrillation which is present in the more advanced stages of mitral stenosis instead of making patients less suitable for operation, seems to have made them more so. This is particularly true if the ventricular rate with auricular fibrillation does not slow satis-

factorily on full doses of digitalis, for we have found that such slowing occurs more readily after operation. The close association of auricular fibrillation with hyperthyroidism and the experimental production of auricular fibrillation in experimental hyperthyroid animals by the injection of adrenalin[4] make one suspect that there may be some relationship between the normal thyroid gland and this arrhythmia.

In all this work, the so-called accidents of heart disease, like pulmonary infarction, peripheral emboli, coronary thrombosis, and hemiplegia, will inevitably occur in one case or another entirely unexpectedly whether operation is performed or not. We have had patients die suddenly a few days before the day set for the operation as well as after the operation. Such distressing possible complications must not be regarded very seriously in estimating the value of the operation or in the selection of cases unless they occur with undue frequency directly after the operation.

Finally in considering congestive heart failure there are two aspects that need clear differentiation, i.e., the subjective and objective evidences of circulatory insufficiency. The subjective symptoms, palpitation and especially breathlessness, frequently precede, by some years, the objective findings of peripheral edema, engorged liver, or moisture in the lungs. The difficulty in interpretation of the subjective complaints is very great because these same symptoms are present without organic heart disease and even when found in patients with obvious valvular disease need be related in no way to circulatory insufficiency. In other words, dyspnea, palpitation, and weakness may occur for many years in cases of well-compensated organic cardiac disease and in some cases will give a false estimate of the duration of congestive failure. The objective criteria, on the other hand, are readily determined and will serve as more reliable guides as to the presence or absence of congestive failure.

The following cases to be reported were more carefully selected. On the whole, the morbid processes were not regarded as so severe as in the first group, but the same criteria discussed above were followed. All the patients were incapacitated and unable to work. All those suffering from angina pectoris had attacks at rest as well as on effort. All those with congestive heart failure gave very little promise of ever being comfortable while ambulatory.

INTERPRETATION OF IMPROVEMENT

The matter of interpreting the results and indicating the degree of improvement is a difficult one. In angina pectoris the disability is very much a subjective one and depends on a variety of different circumstances, such as emotional factors, food intake, temperature changes, and the like. The number of nitroglycerin pills is some guide but not necessarily an accurate one, for the patient may remain suffi-

ciently inactive to avoid attacks. The best single guide is the ability to walk out of doors. Inasmuch as a good many of our patients were operated upon in the fall, their ability or inability to walk during the succeeding unusually cold winter was as severe a functional test as one might have. The results were regarded as excellent if there were no attacks or practically no attacks following operation with the patient ambulatory. Whether they returned to work or not could not be used as a measure of success, because some could find no occupation and others were retired. There are other instances in which they were advised not to resume an active occupation because it seemed wise under the circumstances to rest content with a comparative freedom from attacks. Numerically the term "excellent" might be regarded as 75 to 100 per cent improvement. The result was "good" when the improvement could be estimated as 50 to 75 per cent, "moderately good" as 25 to 50 per cent and "fair" if the amelioration was less than this. Even in the best instances belonging to the excellent group, attacks could recur under unusual circumstances. The same general terminology was used in cases of congestive heart failure, and here again the criteria were somewhat arbitrary and open to personal judgment. If the condition was far advanced and the patient bedridden, the result can be regarded as excellent if the patient is rendered comfortable and ambulatory although he never is able to work. One really has to compare the result obtained with the expectations under usual methods of treatment.

RÉSUMÉ OF CASES OF ANGINA PECTORIS AND CLINICAL RESULTS OF THE OPERATION

This report contains 23 cases* of angina pectoris in which a complete extirpation of a normal thyroid gland was performed. (Table I.) There were 14 males and 9 females. The average age of the males was 60.1 years, the extremes being 42 and 72 years. The average age of the females was 61.7 years, the extremes being 52 and 67 years. The duration of angina pectoris at the time of the operation was 4.6 years for the males and 5.1 years for the females. This series is, of course, rather small, but so far as the figures go the patients here have already lived the average length of life following the onset of angina. In a recent study of 141 fatal cases of angina pectoris[5] it was found that the average length of life after the onset of angina was 4.6 years for the males and 4.5 years for the females. It follows from this that the average life expectancy in the group operated upon is not great. Although nothing is known about the effect of total thyroidectomy on the duration of life in angina, future history of such cases will throw much light on this question. The primary purpose of the procedure

*Case summaries will be published with the reprints.

TABLE

CASE	AGE	SEX	DATE OF OPERATION	DIAGNOSIS	SYMPTOMS
13	60	F.	8/22/33	Angina	8 yr. duration. 2-5 attacks daily.
14	58	M.	9/21/33	Angina	3 yr. duration. 5 attacks daily. Coronary thrombosis 1931-1932.
15	55	M.	9/22/33	Angina	2 yr. duration. 1-300 attacks per week.
16	64	M.	9/22/33	Angina, diabetes, and gallstones	3 yr. duration. Coronary thrombosis. 1931 1-2 attacks daily.
17	42	M.	10/17/33	Angina	12 yr. duration. 100 attacks weekly.
18	60	F.	10/25/33	Angina	1 yr. duration. Coronary thrombosis 1933. Moderate frequency, each 15-30 min.
19	52	F.	10/26/33	Angina, hypertension, and heart failure	4 yr. duration. Nocturnal dyspnea several months. Coronary thrombosis 1931-1933.
20	61	M.	10/28/33	Angina	2 yr. duration. Attacks of moderate frequency.
21	63	M.	10/28/33	Angina and diabetes	3½ yr. duration. Attacks of great severity. 6-10 daily. Coronary thrombosis. June, 1933.
22	61	F.	11/ 1/33	Angina	5 yr. duration. Moderate severity and frequency. Coronary thrombosis 1928.
23	65	F.	11/ 2/33	Angina	10 yr. duration. 10-15 attacks daily.
24	66	M.	11/13/33	Angina	9 yr. duration. 5-10 attacks daily.
25	67	M.	11/22/33	Angina and diabetes	1 yr. duration. Attacks severe and 1 daily.
26	65	F.	11/29/33	Angina	7 mo. duration. Attacks quite severe and very frequent.
27	53	M.	12/ 7/33	Angina	6½ yr. duration. 10 attacks daily. Coronary thrombosis 1932.

*This patient never developed sufficient myxedema to require treatment.

I

BASAL METABOLISM			BLOOD PRESSURE	RESULT	COMMENT
PRE-OPERATIVE	MYXEDEMA	ON THYROID THERAPY			
+12%	-30%	-15%	200/100	Excellent	Only 2 attacks in 10 months. Doing all housework.
- 8	-19	-14	145/80	Excellent	Only rare attacks on severe exertion—8 months.
+ 4	-15	-11	138/86	Excellent	No attacks for 9 months.
+ 8	-24	-	120/54	Moderately good	Much fewer attacks in past 8 months.
-14	-33	-21	130/80	Moderately good	Attacks milder and about ½ as frequent—8 months.
- 3	-28	-14	182/100	Good	Attacks much milder and infrequent—8 months.
+ 8	- 7*	-	140/110	Fair	Attacks much less troublesome but dyspnea persists—8 months.
- 5	-27	-24	120/90	Excellent	For 8 months can walk freely.
- 5	-13	-19	146/92	Fair	For 8 months attacks less severe and less frequent.
- 7	-36	-11	140/70	Excellent	Returned to work, but May, 1934, developed some congestive failure; no angina.
- 9	-28	-22	190/90	Moderately good	For 8 months no attacks at rest, but recur on moderate exertion.
- 6	-22	-27	175/90	Moderately good	Returned to work and for 7 months attacks have been much milder and less frequent.
- 5	-	-	140/80	Died 5 days postoperative	No attacks for 5 days postoperative. Out of bed feeling fine, then had fatal coronary thrombosis.
-11	-24	-25	220/110	Good	For 7 months attacks rare—very mild and none at rest.
-18	-32	-24	110/68	Excellent to fair	For 6 weeks no attacks, then they recurred before thyroid extract was started. 4 months postoperative fatal acute coronary thrombosis.

TABLE

CASE	AGE	SEX	DATE OF OPERATION	DIAGNOSIS	SYMPTOMS
28	61	M.	12/ 8/33	Angina, transient auricular flutter	7 yr. duration. Attacks ver severe—4 daily.
29	67	F.	12/13/33	Angina	12 yr. duration. Attacks ver severe and 5-6 daily.
30	65	M.	12/13/33	Angina	1 yr. duration. 6-7 attack daily.
31	62	F.	1/ 4/34	Angina	15 mo. duration. Attacks ver severe and frequent. Nitr glycerin ineffective.
32	54	M.	1/17/34	Angina	9 yr. duration. 2 attacks daily.
33	64	F.	1/20/34	Angina	3 yr. duration. Attacks of moderate severity and frequency.
34	56	M.	3/ 5/34	Angina and myocardial failure	4 yr. duration. Coronary thrombosis. 1931. Attacks moderate frequency and severity.
35	72	M.	3/ 6/34	Angina and paralysis agitans	9 mo. duration. Attacks 2-3 daily. Very severe. Nitroglycerin ineffective.
36	33	M.	10/16/33	Mitral stenosis, aortic insufficiency, and auricular fibrillation	Dyspnea 5 months. Progressively worse, finally marked failure.
37	54	M.	12/ 6/33	Mitral stenosis, auricular fibrillation, emphysema, and duodenal ulcer	Dyspnea 3 yr. Marked decompensation 1 week.
38	40	M.	1/13/34	Mitral stenosis, depressive psychosis	Increasing dyspnea 4 yr. Attacks acute pulmonary edema. Psychosis.
39	39	F.	1/27/34	Mitral stenosis, auricular fibrillation	Dyspnea 7 yr. Frequent decompensation.
40	50	M.	2/ 8/34	Chronic myocarditis, auricular fibrillation, emphysema	4 attacks of decompensation in 11 yr.
41	44	M.	2/12/34	Mitral stenosis, aortic insufficiency, auricular fibrillation	7 yr. increasing dyspnea.
42	30	F.	2/13/34	Mitral stenosis, aortic insufficiency	3 yr. increasing dyspnea. In bed 3 months.

—CONT'D

BASAL METABOLISM			BLOOD PRESSURE	RESULT	COMMENT
PRE-OPERATIVE	MYXEDEMA	ON THYROID THERAPY			
+ 8	−29	− 5	160/110	Excellent	No attacks for six months.
− 9	−	−	150/90	Died 1 day post-operative	Patient begged for relief. Attacks unbearable. Fatal acute coronary thrombosis 1 day postoperatively.
+ 1	− 9	0	178/100	Good	Only occasional attacks for 6 months mainly because he is more active.
− 4	−	−	180/110	Died 1 day post-operative	Fatal acute pulmonary complication 1 day postoperatively.
− 3	−21	−	134/80	Good	Attacks only on severe exertion 6 months.
+15	+ 3	+ 3	218/100	Good	Attacks on moderate exertion 4 months.
− 4	−28	−23	130/85	Excellent	No attacks. Walking freely 3 months.
+ 7	−20	−	160/80	Excellent	No attacks 3 months.
− 1	−31	−21	140/90	Excellent	Ambulatory. Working. Symptom-free 8 months.
− 6	−22	−36	140/80	Good	Ambulatory. Comfortable 5 months. One slight break in compensation.
+22	−	−	120/80	Failure	Died Feb. 16, 1934. Mesenteric thrombosis, acute pulmonary edema.
+16	−21	− 7	125/90	Excellent	Does housework without symptoms—6 months.
+21	−21	−15	130/90	Fair	Subjective improvement. Ambulatory.
− 9	−30	−18	120/96	Excellent	4 months ambulatory. Working.
+15	−19	−16	122/64	Good	4 months ambulatory. Dyspnea on moderate exertion.

was relief of anginal pain, for it is already known that subsequent coronary thrombosis is not prevented by total thyroidectomy.

The clinical results in the relief of anginal pain were divided into four gradations according to the method explained above: excellent, good, moderately good, and fair. Among these 23 patients there were 2 which were regarded as postoperative deaths. Another patient died five days after operation of typical coronary thrombosis, having been entirely free from pain during the interval, and a fourth who had an excellent result for six weeks followed by a recurrence of anginal pain of moderate degree, finally died four months after the operation of acute coronary thrombosis. Of the remaining 19 who are all still alive, the results were "excellent" 8, "good" 6, "moderately good" 4, and "fair" 1. In three of these there were varying degrees of congestive heart failure in addition to angina pectoris, of which two have remained free of these symptoms and one has had increasing myocardial failure. The average duration of follow-up observation on the 19 living patients is six months, the longest is over ten months, and the shortest over three months.* Considering the fact that these patients were selected only because their symptoms were refractory to the ordinary methods available, that the attacks came at rest as well as on effort, and that the attacks were sufficiently crippling to make life hardly worth while, it is fair to consider that the results were quite satisfactory.

Observation on the Basal Metabolic Rate

The preoperative basal metabolic rates in these cases varied a good deal. The average was +1 per cent. The extremes were −18 per cent and +15 per cent. We have learned from experience of the past two years that there are occasional individuals showing basal metabolic rate of +20 per cent to +45 per cent, with no clinical signs of hyperthyroidism, in whom the thyroid gland is normal on gross and microscopic examination. Such cases have been found in which the high rate could not be accounted for by dyspnea or psychic influences. This occasionally may lead to confusion in preoperative diagnosis, as at times it has been impossible to predict whether we were dealing with a case of masked hyperthyroidism or a cardiac with a normal thyroid gland.

The speed with which the basal metabolic rate fell after operation was not constant. Thyroid gland was administered to these patients when they first began to complain of symptoms pointing to myxedema. The average metabolic rate at this point was −23 per cent. There

*Since this paper was submitted, three of the patients have died: one (Case 16), one day after cholecystectomy, of coronary thrombosis; and two others (Cases 23 and 33), of coronary thrombosis. The intervals after thyroidectomy were ten, sixteen, and twelve months, respectively. All those with congestive heart failure are still living. The follow-up period is now nine months longer than the time mentioned in the text.

were other evidences of the hypothyroid state before this point was reached, such as a pallor or a change of facial expression and hypercholesterinemia. But if the time at which it seemed advisable to administer thyroid gland is taken as an index, the average interval after operation was found to be 65.4 days; the longest was 94 days and the shortest 38 days. The average metabolic rate after thyroid extract was administered was –16 per cent. At first glance one might expect that those with a lower preoperative basal metabolic rate would develop myxedema more rapidly than those with a high rate. No significant difference was found, however, in this study. The average time of the former group with an average basal metabolic rate of –8 per cent was 64.2 days and of the latter with an average basal metabolic rate of +10 per cent was 67.1 days. It is of some interest that in occasional instances the basal metabolic rate had fallen but very little even one to two months after the operation. One patient with a preoperative reading of +15 per cent had a basal metabolic rate of +3 per cent 48 days after total thyroidectomy. At this time there were some clinical evidences of myxedema such as dryness of the skin and somnolence and the blood cholesterol had risen to 610 mg. per cent. The administration of thyroid gland was begun at this point despite the absence of a low metabolic rate. Another patient showed a similar course. These variations in the fall of the metabolic rate are probably dependent upon variations in the speed in which the remaining thyroid substances disappear from the body and on variations in the balance of the other endocrine glands. In none of the cases was the metabolic rate allowed to reach the very low levels seen in spontaneous myxedema. Attention has recently been called by Means and Lerman[6] to the variations in the time at which different aspects of the hypothyroid state may be expected to develop after the function of the thyroid gland has been impaired. It is likely that the so-called "myxedematous heart" requires years for its development, and the same may be true of secondary anemia. Whether such ultimate changes will occur in these patients in whom the very low levels of metabolism are prevented by the feeding of thyroid extract is problematic though unlikely. In general, an attempt was made to keep the metabolic level of these cases around –20 per cent.

Velocity of Blood Flow

Measurements of the velocity of blood flow in patients with angina pectoris operated upon can reflect fairly clearly the effect of artificial myxedema on the speed of circulation. In these the element of congestive heart failure with its accompanied slowing of the circulation does not necessarily exist. The average preoperative rate of blood flow measured by the sodium cyanide method[7] in these 23 cases was 20 seconds (average basal metabolic rate +1 per cent). Four days

after the operation when the average basal metabolic rate was −1 per cent the average circulation time was still 20 seconds. When symptoms of myxedema were sufficient to warrant treatment (65 days postoperative), the average basal metabolic rate was −25 per cent and the circulation time was 32 seconds, i.e., approximately a fall of ½ second for each 1 per cent drop in the metabolic rate. The approximation is in accord with the readings obtained in a group of patients after the administration of thyroid gland. As the basal metabolic rate rose to an average level of −14 per cent the speed of circulation increased to an average of 26 seconds. Unlike the observations to be discussed below in cases of congestive heart failure, every case of angina showed consistent slowing of the speed of circulation after operation as the basal metabolic rate fell. This is in accord with the findings of Blumgart and his coworkers[8] in spontaneous myxedemas.

Changes in Blood Cholesterol

Determinations of the cholesterol content of the blood were made on 11 cases of angina pectoris. The method of Bloor was used; and although the control figures seemed higher than those given for normal individuals, the changes detected were sufficiently great to be of distinct significance. The average finding before operation in this series was 244 mg. per cent. The high normal figure may be due to the age of these patients, or it may be related to the fact that they all had vascular disease. The second determination was made about five days after the operation, and the average was found to be 260 mg. per cent. At the point of clinical myxedema this figure had risen to 488 mg. per cent and then subsequently fell to an average of 329 mg. per cent as a result of the administration of thyroid extract. In practically all instances, the cholesterol content of the blood is continuing at a higher level than before operation. This is apparently a necessary result of our attempt at keeping the metabolic rate around −20 per cent. These findings are in general in accord with those published by Mason, Hunt and Hurxthal[9] in spontaneous myxedema. Whatever ultimate deleterious effect this hypercholesterinemia may have, will become apparent only in the future study of these cases.

Changes in the Size of the Heart

Careful measurements of the size of the heart as determined by roentgenograms taken at a distance of seven feet were made in ten of the patients with angina pectoris. The distance of the right and left borders from the midline (Mr. and Ml.), the diameter of the aortic shadow (G.V.), the internal diameter of the chest (I.D.) and the transverse diameter of the heart (T.D.) were charted. The average preoperative figures when the basal metabolic rate was +1 per cent were Mr. 4.4 cm., Ml. 9.4 cm., G.V. 5.7 cm., I.D. 28.7 cm., and T.D. 13.8 cm.

About two months after operation when symptoms of myxedema were present (basal metabolic rate –26 per cent), the corresponding average figures were Mr. 4 8 cm., Ml. 10 0 cm., G.V. 6.0 cm., I.D. 29.2 cm., and T.D. 14.8 cm. From these figures it seems that the average transverse diameter of the heart increased by 1 cm. This increase occurred both on the right and on the left side of the heart about equally. The increase in the size of the aortic shadow was only 0.3 cm. and may be within the limit of error. Further observations were made about two months later after the basal metabolic rate had been raised to an average level of –12 per cent. Average measurements at this time were as follows: Mr. 4.8 cm., Ml. 10.4 cm., G.V. 6.1 cm., I.D. 29.1 cm., and T.D. 15.2 cm. The transverse diameter of the heart at the time these last measurements were taken on the average of 141 days after the operation, showed a very slight further increase. The figure was then 1.4 cm. greater than that of the preoperative diameter. The slight increase continued despite the rise in the basal metabolic rate brought about by thyroid extract. These changes cannot be regarded as insignificant despite the fact that the average internal diameter of the chest also increased 0.4 cm. over the preoperative level. It can be regarded either that this latter increase was within the error of measurement or that the chest was held in a more expanded condition after than before operation. One is led to suspect that a slow, steady dilatation is taking place in these patients as a result of prolonged, mild myxedema which is not entirely compensated for by the small doses of thyroid extract.

Observation on the Blood Pressure

The preoperative level of the blood pressure in these 23 patients with angina pectoris varied a great deal. There were some with hypotension and others with marked hypertension. The average pressure was systolic 152 mm. and diastolic 90 mm. The extremes for the systolic pressure were 120 mm. and 225 mm., and for the diastolic 68 mm. and 150 mm. About one week after the operation the average systolic was about 141 mm. and diastolic 82 mm. The fall in the level of blood pressure can be ascribed either to the continued rest in bed or as a result of the removal of the thyroid gland. It cannot be due to a fall in the metabolic rate for this had not as yet occurred. About two months after the operation when symptoms of clinical myxedema were present, the average systolic pressure was 167 mm. and the average diastolic was 96 mm. The patients were now ambulatory, and the slight rise over the preoperative level can easily be explained on this basis. After a period of almost six months had elapsed following the operation, the average readings were systolic 163 mm. and diastolic 93 mm. In general it can be said that although there may be a slight tendency for the blood pressure to rise, no significant variations have been detected over an average period of six months.

Changes in Weight

It is well known that with the hypothyroid state there is a tendency to gain weight. This proved to be true in these cases of angina pectoris. The average preoperative weight of 11 patients was 67.4 kg. About two months later when they had clinical evidence of myxedema, the average weight was 72.0 kg. Six months after operation, although they had all been taking small doses of thyroid extract so that the basal metabolic rate had increased somewhat from the previous low level, the average weight was 73.2 kg. Inasmuch as none of these patients had congestive heart failure, the gain of almost 6 kg. in six months cannot be ascribed to the type of water retention that accompanies congestive failure. It must be interpreted as a direct result of the maintained lowering of the basal metabolism. Furthermore the increase in weight was not retarded by the small doses of the thyroid extract which it seemed desirable for them to take.

Possibility of Secondary Anemia

One of the recognized accompaniments of spontaneous myxedema is a secondary anemia.[10] Although it is more likely that this sort of anemia develops only after the myxedema has continued for some years, it is naturally of interest to know whether blood changes of this type developed in our cases in which artificial myxedema was produced. Careful estimates of the hemoglobin and erythrocyte counts were made in eleven cases. The preoperative figures for these two determinations were respectively 85 per cent and 4.8 millions. At an average interval of 96 days after operation the corresponding figures were 87 per cent and 4.7 millions. It is evident that during this brief period anemia had not developed. In a few instances examinations as long as nine months after operation failed to show any development of anemia. It would not be surprising if this did occur in some of these patients after a lapse of years.

Observations on the Vital Capacity of the Lungs

There is nothing inherent in the mechanism of angina pectoris which diminishes the vital capacity of the lungs. When the vital capacity in this condition is compared to the customary normal standards, it has been found to be somewhat diminished,[11] primarily because a fall is to be expected normally with advancing years. Furthermore in myxedema unaccompanied by congestive heart failure, dyspnea is not an integral symptom and the vital capacity is therefore unchanged. Observations on this series of cases confirm the above impressions. The average preoperative vital capacity of 18 patients was 2,630 c.c. About one week after operation the figure was 2,590 c.c., two months later when clinical evidence of myxedema was present it was 2,670 c.c., and

about two months after this following the administration of thyroid extract it was 2,600 c.c. In a word, the vital capacity of the lungs remained unchanged in cases of angina pectoris following thyroidectomy.

Changes in the Electrocardiograms

Frequent reference has been made to changes in the electrocardiogram which characterize spontaneous myxedema. Essentially they consist in a diminution of all electrical complexes both auricular and ventricular with particular flattening of the T-waves. Like many other bodily changes which result from myxedema, these alterations probably require years for their production. During the comparatively short period that the patients in this study have been observed, no such marked findings have been noted. In some there was slight but distinct lowering of the amplitude of the QRS complex and the T-waves. In a few the P-wave was also diminished. Occasionally no significant changes were detected. It is likely that because these patients are not permitted to remain in a state of marked myxedema, the characteristic electrocardiographic evidences of "myxedema heart" did not supervene.

RÉSUMÉ OF PATIENTS WITH CONGESTIVE HEART FAILURE AND CLINICAL RESULTS OF THE OPERATION

In the second series of cases reported here there were seven cases* of congestive heart failure, five males and two females. The average age of the former was 44 years and of the latter 35 years. Six had mitral stenosis, of which four had auricular fibrillation and two had a regular rhythm (one of the latter had paroxysmal auricular flutter). Three of these valvular cases had additional involvement of the aortic valve with aortic regurgitation. There was one nonvalvular case in which there were myocardial failure and auricular fibrillation associated with a previous hypertension. The average duration of symptoms which we regarded as evidences of congestive heart failure was 4.8 years. This figure would have been shorter except for one patient who had a history going back for eleven years. The duration of objective evidence of congestive heart failure must have been distinctly less than 4.8 years, but it is impossible to determine this figure exactly. We estimated the improvement as excellent in three of these cases (No. 36, 39 and 41), good in two (No. 37 and 42), fair in one (No. 40), and as absent in one (No. 38). The three regarded as excellent have remained free from objective and subjective evidences of circulatory failure while ambulatory for intervals of eight months, six months, and four months. The others have had varying degrees of improvement. In the one case classified as a failure the patient died five weeks after operation of acute pulmonary edema following a mesenteric thrombosis. Even this patient, judged by his ability to breathe, had improved

*Case summaries will be published with the reprints.

shortly after operation. The one that seems to have had the least benefit was the nonvalvular patient with a history of dyspnea of eleven years' duration. Although recurrent edema and some ascites have developed, the factor of breathlessness has improved; for, whereas before operation he was orthopneic, he can now lie flat.

A general survey of the cases of congestive heart failure and those reported in the first series confirms our earlier impression that complete thyroidectomy is not so helpful in this condition as it is in angina pectoris. To be sure, it is not a simple matter to judge the result of treatment and the progress of congestive failure, because factors like intercurrent infection, infarction, and other so-called unexpected accidents of heart disease, may suddenly change the clinical picture. Furthermore, the inherent progress of the disease varies so much in speed that in some cases it may quickly overtake the benefits derived from the operation. At the present time, the exact factors that determine the choice of patients with congestive heart failure are not clear. Although one prefers those cases that become free of objective evidence of failure on the preoperative medical care, we have had several instances in which the liver was still markedly enlarged and recurrent hydrothorax was still present, only to see these entirely disappear within ten days after operation.

The average preoperative basal metabolic rate in these seven cases was +8 per cent; they varied from −9 per cent to +22 per cent. The average rate when thyroid extract was first administered for myxedema was −24 per cent (an average of 68 days after operation). About ten weeks later, on thyroid medication the basal metabolic rate was −18 per cent. Although the desirable level varies somewhat with different patients, this last figure is approximately the optimum.

It has been shown that the velocity of blood flow is slowed in congestive heart failure and accelerates with improvement of the state of the circulation.[12] The last preoperative reading of these cases showed an average of 31 seconds. The basal metabolic rate at the time these readings were taken was +7 per cent. About two months later the basal rate was −26 per cent. The average circulation time was 40 seconds. This indicated an average slowing of the circulation of 9 seconds, accompanying a fall in metabolism of 33 per cent. The degree of slowing here was only half as great per unit fall in metabolism as that which occurred in patients with angina pectoris but without congestion. It is very significant that the patient (Case No. 36) who showed one of the most striking instances of improvement following operation was the only one who actually had an increase in the speed of circulation. The circulation time fell from 41 to 20 seconds as the metabolism fell from −4 per cent to −31 per cent. It is perfectly clear that unlike the anginal group, changes in the velocity of blood

flow in congestive heart failure subsequent to complete thyroidectomy are by no means constant. Similar inconsistencies between the basal metabolic rate and the velocity of blood flow are apparent on careful examination of the charts published by Blumgart and his coworkers.[13] One is quickly impressed by the fact that the degree of slowing of the circulation depends in a large measure upon the rate of blood flow before operation. When this rate is normal as in angina pectoris, a very consistent slowing occurs. Such slowing also results in some patients who have congestive heart failure but in whom the rate is approximately normal before operation. When the preoperative circulation time is considerably prolonged, however, if further slowing occurs it is only slight and there may be essentially no change or the rate may increase. The whole matter of the velocity of blood flow, although one factor in circulatory dynamics, is difficult of interpretation for it is so intricately dependent upon the total blood volume which shows considerable alterations during congestive failure.

It has long been known that the vital capacity of the lungs is diminished in congestive heart failure and increases as compensation improves. In these seven patients the preoperative vital capacity of the lungs was diminished, for the average was 2,100 c.c. At the point when clinical myxedema first was present, the reading was 2,190 c.c., and this rose slightly in a few months to 2,260 c.c., following the administration of thyroid extract. In two of these cases there was an increase of 600 c.c. or more following the operation, but on the whole one can say that the average change was very slight despite the fact that there was a decided improvement in the element of subjective dyspnea. In other words this method of treatment enabled the patient to breathe more comfortably, although the actual breathing space was essentially unaltered. The reason for this is probably that the needs for oxygen have been diminished and that the sensitivity of the nervous system was altered.

The changes in the size of the heart which took place in these cases, as measured by roentgenograms, were inconstant. The average transverse diameter before operation was 17.1 cm. when the basal metabolic rate was +3 per cent. Eighty-five days later when the average basal metabolic rate was −21 per cent, the transverse diameter was also 17.1 cm. Seventy-four days later when the average metabolism had risen to −16 per cent, as a result of the administration of thyroid extract the transverse diameter was 17.2 cm. In one case (No. 36) the heart size diminished 2.4 cm. and in another (No. 42) increased 1.2 cm. at the time of clinical myxedema. In contrast to patients with angina pectoris this group showed no consistent enlargement of the heart as the state of moderate myxedema continued. One may infer from this that with the improvement that takes place following thyroidectomy in cases of congestive heart failure there is a

tendency to diminution in the size of the heart which offsets the dilatation which would otherwise occur from myxedema.

The average preoperative blood pressure was 113 mm. systolic and 73 mm. diastolic. When the patients first had clinical evidences of myxedema the readings were 128 mm. systolic and 84 mm. diastolic, and at an average period of about five months later the blood pressure was essentially the same—129 mm. systolic and 78 mm. diastolic.

RATIONALE OF TOTAL THYROIDECTOMY AND DISCUSSION

For some years it has been apparent to many clinicians that the lowering of the basal metabolism exercises a beneficial effect on an embarrassed circulation. This has been true whether the circulatory failure was of the congestive or of the anginal type. The most outspoken evidence of this effect was witnessed in the extraordinary improvement that followed subtotal thyroidectomy in those patients with exophthalmic goiter or toxic adenoma who also showed gross cardiac disability. In fact, a considerable improvement was generally apparent concomitant with the fall of the basal metabolism that followed the administration of Lugol's solution, even before subtotal thyroidectomy. From a diametrically opposite direction there has been considerable clinical experience that also leads to the same conviction, i.e., that the state of the thyroid gland and the basal metabolism have a profound effect on the heart. It was frequently observed that cases with myxedema might easily develop angina pectoris or congestive failure as the metabolism would rise on thyroid administration.[14, 15, 16] The first instance of this we recall seeing was in 1925 when in a patient with myxedema the number of attacks of angina could be controlled entirely by the amount of thyroid he was given. When the metabolism was allowed to remain around –37 per cent, there were no attacks but there were symptoms of myxedema; and when it was –5 per cent there were frequent anginal attacks, with no clinical evidence of myxedema. It was found in this case that –15 per cent was about the optimum level. This relationship was currently known by many physicians who were specially interested in either thyroid or heart disease. Christian[15] in fact epitomized the situation in the statement that "thyroid deficiency may be a conservative process, a form of cardiac rest, that is advantageous to the heart."

Simultaneously considerable attention was also being paid to that small but fortunate group of cardiac cripples who had masked or latent hyperthyroidism. Here were patients suffering from advanced disabling heart disease who formerly succumbed because, although they had active hyperthyroidism, evidence of this was so obscure that it remained entirely overlooked. When such cases were properly diagnosed and the patients properly treated, it was found that many could be restored to very useful lives. This comparatively small group with

masked hyperthyroidism interested us intensely at the Peter Bent Brigham Hospital and formed the material for a series of clinical studies[1, 17, 18] which emphasized the importance and discussed the methods of arriving at the correct diagnosis.

Amid this enthusiastic search for masked hyperthyroidism among patients suffering from organic heart disease one patient was subjected to subtotal thyroidectomy in 1927 in whom the gland proved to be normal both in gross and in microscopic examination. Despite this a most extraordinary improvement followed which had not been obtained by all the customary measures employed before in this case. This fortuitous experience led to the inference that subtotal thyroidectomy of a normal gland might be helpful in the treatment of intractable heart failure. As time went on and this patient continued to be free from congestion, it seemed to warrant a conclusion then drawn that "the occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive failure, in whom the thyroid gland was normal, suggests that this operation may be useful more generally in the treatment of various forms of cardiac disease."[1]

Following this, deliberate removal of the thyroid gland was undertaken both at the Beth Israel Hospital and at the Peter Bent Brigham Hospital, in cardiac cases that were not responding to the routine methods of treatment. When it was found that in some of the cases in which a subtotal thyroidectomy was performed, clinical improvement and the simultaneous fall in the basal metabolic rate were only temporary, it was assumed that the remaining part of the gland could either regenerate or increase its activity.[3] The operation which was adopted for subsequent work therefore was a total thyroidectomy, the first one of which (Case 3, first series) was performed at the Peter Bent Brigham Hospital by Dr. E. C. Cutler, December 14, 1932. That such regeneration does not always occur after a subtotal thyroidectomy is illustrated by Case 4 of reference 3. Here, after nine-tenths of the gland was removed not only did the angina pectoris disappear but myxedema supervened, which has required constant thyroid medication for the past sixteen months.

Physiological studies on the circulation in heart failure and in disease of the thyroid gland were available to lend some support to the validity of this method of treatment. Particularly was this true of the observation on the velocity of blood flow by Blumgart and his associates.[8] It was found that congestive heart failure was accompanied by a slowing of the rate of blood flow and that with improvement the rate of blood flow accelerated. It was also found that in myxedema the rate of blood flow was slow in the absence of congestive failure. The conclusion that may be drawn from these observations is that with

a lowered metabolism the slow speed of the blood is adequate, and whether heart failure results in any case is a question of demand and supply, of the basal metabolic needs on the one hand and the rate of blood flow on the other. The therapeutic inference from this is that, when congestive failure is present, removing the thyroid gland may diminish the demand on the heart so that with a lowered metabolism the slow circulation will be adequate and compensation will be restored.

In this discussion it was hinted that the velocity of blood flow is a measure of the work of the heart. It may be an indirect index but hardly can be regarded as the accurate guide of the work of the heart. Better criteria would have been the volume output, the pressure relations, and rate at which the heart beats. Furthermore the prevailing conceptions concerning the mechanism of heart failure have been conflicting. The most recent work of Harrison and his associates[19] has shown that improvement in heart failure is independent of volume output of the heart. The latter may increase, decrease, or remain the same, the essential change being an improvement in the back pressure factor, i.e., diminution of venous or pulmonary engorgement. In fact they found that improvement in one case following total thyroidectomy was accompanied by a diminution in volume output of the heart. This is not in accord with the theoretical consideration of Blumgart and his coworkers[13] who stated that "if the normal metabolic rate of the patient with congestive failure were reduced, his blood supply while not necessarily altered, might nevertheless be sufficient for the lowered needs of the body."

Although one might offer the above explanation for the possible benefits to be derived from thyroidectomy in congestive heart failure, there is a distinct fallacy in these predictions. If in myxedema the rate of blood flow is slowed as a result of the lowered metabolism, would one not have to postulate that when myxedema is produced surgically for congestive heart failure, which already has a slow circulation, the speed of blood flow would be further slowed? The result which one should logically have expected is a diminution in both the demand and the supply, efficiency of the circulation remaining as before. That such has not been found to be the case since the postoperative results have been analyzed does not preclude the fact that it was not predictable on the early physiologic work. Moreover the statement[13] that "with arteriosclerotic narrowing of the coronary vessels, the blood supply of the heart through these vessels may be inadequate to the needs of a normal metabolic rate although sufficient for the needs of the heart at lower metabolic rates" overlooks the fact that the slowing of the blood flow and the diminution of volume out-

put of the heart that accompanies myxedema would tend to decrease the blood supply through these same narrowed coronary arteries.

Theoretically one might have said that it would be desirable to lower the basal metabolism and at the same time maintain the rate of blood flow unchanged or to speed it up. It is clear that the only effect that could have been anticipated from the physiological studies was a further slowing of the circulation which might be harmful. May it not be that improvement will be determined by just this differential effect? When the fall in metabolism is accompanied by less than the expected slowing of blood flow, improvement should occur. As a matter of experience the velocity of blood flow has shown no constant relationship to the fall in the basal metabolism. At times when there were congestive failure and a very slow velocity of blood flow before operation, the flow remained unchanged after operation, even when the metabolism was −30 per cent, in the face of clinical improvement. When the circulation time was normal or essentially normal, as in the cases of angina pectoris and those cases of congestive heart failure which became well compensated before operation, there always was a distinct slowing of the blood flow which accompanied the fall in the basal metabolic rate. Why these different results occurred has not been thoroughly explained, although it may be that in congestive heart failure an improvement in the efficiency of the circulation following the operation brought about by some unknown mechanism of itself tends to speed up the circulation and thereby counterbalance the slowing effect that would otherwise result from the artificial myxedema.

Furthermore, the early observations on the rate of blood flow on congestive heart failure were not applicable to cases of pure angina pectoris, for here there is no congestion nor is there any slowing of blood flow. In angina it was not a matter of lowering the metabolism to meet the slow circulation. Particularly is this true of those patients who have attacks of angina at rest. Such cases seem to have some internal mechanism that explodes or acts as a trigger in precipitating attacks. Whether this is dependent on a temporary increase in the rate of blood flow has never been determined. There is much presumptive evidence that the mechanism, whatever it may be, is linked up with the adrenals.

Clinically it has been observed that certain cardiac disturbances which were in some way related to the thyroid gland were independent of the basal metabolism. Wilson and his associates[20] called attention to instances of transient auricular fibrillation occurring in patients with a normal metabolism who only subsequently developed an elevation of the basal metabolic rate and in whom the cardiac abnormality disappeared after subtotal thyroidectomy. Likewise, Coller[21] found that certain cardiac irregularities in nontoxic goiter disap-

peared after subtotal thyroidectomy although the metabolism was normal. Furthermore, it was noted in this present investigation that in patients who had daily and frequent attacks of angina, such attacks disappeared directly after the thyroidectomy, at a time when the basal metabolic rate and the rate of blood flow were still the same as they were before operation. Many patients volunteered the information that within a few days after total thyroidectomy they were less heart conscious and that mild nonanginal discomforts around the heart disappeared. From all this it was predicted that removing the thyroid gland causes a fundamental alteration in the response of the heart to adrenalin. This has since been found to be true both clinically in our cases and experimentally in animals. It has been shown that adrenalin reproduced attacks of angina if injected before operation[22] and failed to do so the second or third day after total thyroidectomy.[23] Furthermore, certain irregularities of the heart can be produced by the injection of adrenalin into rabbits that are made hyperthyroid that do not occur with similar doses in normal or thyroidectomized animals.[4] Likewise recent animal experiments have shown that there is a fundamental difference in the response of the heart to injected or secreted adrenalin after total thyroidectomy.[24] The acceleration of the heart following the same stimulus is lessened 30 to 60 per cent by such an operation. All these observations indicate that the removal of the thyroid gland alters the sensitivity of the heart to adrenalin, and confirms opinions long since expressed that the thyroid gland enhances the adrenalin effect on the body.[25, 26] These considerations are pertinent in indicating that the early theoretical data which have been supposed to be the starting point of this new operation need some revision, notwithstanding the fact that subsequent studies seem to validate this therapeutic procedure.

Very recently an investigation to explain early relief of pain in angina pectoris was published by Weinstein and his associates.[27] They presented some evidence to show that the early relief was due to the severance of nerves during the operation and that this effect was only temporary. Although it is impossible to refute these results without reproducing the experiments performed in that research (especially deliberate hemithyroidectomy), we are of the opinion that their explanation is not valid. It seems unlikely that there can be enough cardiac nerves in the operative field to account for results we have witnessed. Furthermore, the disappearance of hepatic engorgement during the first seven to ten days following operation, which we and others have observed to occur before any appreciable fall in basal metabolic rate, cannot be explained on the basis of section of cardiac nerves. At any rate much more work will be necessary to account for the effects on the circulation that follow total thyroidectomy.

Finally in considering the rationale of complete thyroidectomy one naturally must pay due regard to the possible harmful effects. When it is appreciated that the operation is proposed for conditions that are inherently progressive and that do not respond satisfactorily to the ordinary available measures, one may be ready to accept some comparatively minor handicaps that might result. The possibility of postoperative myxedema is not very material, for the administration of thyroid gland can undo, if it were desirable, most if not all the deleterious effects of this type. The danger of parathyroid tetany has been insignificant, for whatever minor symptoms of this deficiency have occurred have been readily controlled. Injury to the recurrent laryngeal nerve is a technical problem, and so far has given rise to very little concern. The operative mortality, had it been high, would have been a serious handicap. Realizing that the life expectancy in the patients subjected to this operation is not great and that sudden fatalities or other disastrous complications are the expected events in these conditions, the operative mortality of 5 to 10 per cent cannot be regarded as excessive.

The medical management of all these cases has recently been discussed[28] and need not be gone into here. There is one point, however, that needs comment. It has been urged[27] that patients with angina pectoris should be kept strictly in bed until a significant fall in the basal metabolism has occurred, because the early relief of pain was regarded as merely due to the severance of nerves. This may require several weeks of bed care in some cases, and it is no more logical than it would be to advise a patient with angina pectoris who obtained relief following cervical sympathectomy or alcohol injections of the thoracic ganglia to stay in bed for the entire time that he remains free from pain, which may be years. We have, therefore, allowed patients with uncomplicated angina to become ambulatory from a few days to a week after the operation.

SUMMARY

1. A follow-up study was made of twelve cases of severe intractable heart disease previously reported in which thyroidectomy was performed. This showed that although some benefit was obtained, the state of the lesions was so far advanced that in most cases improvement did not last an appreciable length of time.

2. A second series of thirty cases of patients also suffering from chronic intractable heart disease is now reported. There were twenty-three patients with angina pectoris and seven with congestive heart failure. Six of the latter had mitral stenosis and one was a nonvalvular case. They were all incapacitated to various degrees.

3. There were two surgical fatalities among these thirty cases, both in the anginal group. One additional patient died of typical acute coronary thrombosis five days postoperatively after he was feeling quite well and was ambulatory. A fourth died of coronary thrombosis four months after the operation, having obtained considerable improvement in the preceding three months. Of the remaining nineteen, all are still alive an average length of six months after the operation. Improvement was regarded as "excellent" in eight, "good" in six, "moderately good" in four, and "fair" in one.

Among the seven cases of congestive failure there was no surgical mortality. One patient died about five weeks after operation of mesenteric thrombosis and acute pulmonary edema. In three the result was "excellent," in two it was "good," and in one it was "fair."

4. The criteria for selection of cases were discussed. At present, there still remains some uncertainty as to the exact type of case with congestive heart failure that is suitable for this procedure.

5. Observations were made, particularly in the cases with angina pectoris, of the following factors: the basal metabolic rate, the velocity of blood flow, the cholesterol content of the blood, the size of the heart, the blood pressure levels, the possibility of secondary anemia, the body weight, the vital capacity of the lungs, and the electrocardiograms.

6. The rationale of this procedure and some theoretical considerations that underlie it are discussed. It was thought that apart from the main effect of thyroidectomy in diminishing the work of the heart by decreasing the basal metabolic rate there was an additional important effect, i.e., the diminution in the sensitivity of the heart to adrenalin.

7. The results obtained in this study indicate that total thyroidectomy produced specific clinical improvement in cases that were refractory to the ordinary methods of treatment. This seemed to be much more definite in those with angina pectoris than in those with congestive heart failure. This operation should be undertaken, however, only after the most careful consideration of the diagnosis and prognosis. Furthermore, it must be evident that ordinary medical management has failed and that the operation is likely to result in improvement that is otherwise unobtainable.

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CORONARY ARTERIOSCLEROSIS, CORONARY THROMBOSIS, AND THE RESULTING MYOCARDIAL CHANGES

An Evaluation of Their Respective Clinical Pictures Including the Electrocardiographic Records, Based on the Anatomical Findings*†

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(Continued from page 595 of June issue)

DISCUSSION OF THE ANATOMICAL FINDINGS

References to the literature of anatomical lesions are only occasionally given in this discussion. The articles by Kirch,[7] by Benson[8] and by Karsner,[6] should be consulted for a review of the more modern literature of this subject.

In the present series, as mentioned previously, all major branches of the coronary arteries were carefully dissected with small scissors and the lesions in each heart recorded in a separate diagram. Fig. 1 shows a diagram of the course of the coronary arteries adapted from illustrations given by Spalteholz[9] and by Gross[10]‡ with the nomenclature of the coronary branches as used by Spalteholz.§ This diagram served as a model for the individual diagrams accompanying the case reports.

Types of Lesions in the Coronary Arteries.—The most commonly encountered lesions were marked fibrosis, hyalinization, calcification, and thrombi. The various stages of coronary sclerosis described by Bork[11] were encountered with the exception of the first, the earliest stage. There was marked intimal hyperplasia with lipoid deposits, atheromatous formations, and calcification of the intima and to a lesser extent of the media. No attempt was made to differentiate between occlusions resulting from hyalinized and calcified plaques and so-called connective tissue occlusions as described by Koch and Kong[12] because of the impossibility of differentiating the latter type of occlusions from those caused by organized thrombi. Table I gives a summary of the types

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‡We are indebted to Dr. N. Mitchell for making this diagram for us.

§Instead of right coronary artery, the term "right circumflex branch" is used to signify the homologous character of this vessel to the circumflex branch of the left coronary artery.

of lesions in the various branches of the coronary arteries. Recent thrombi of the coronary arteries were found 18 times, while organizing and old thrombi were encountered in 14 instances. Occlusions by calcified plaques were encountered 13 times. Every heart showed more than one occlusion or marked narrowing of the coronary arteries. In some instances as many as four lesions were found in the coronary arterial system in a single heart. This emphasizes the importance of dissecting all main branches of the coronary arteries even after one occluding lesion has been demonstrated.

There was no relation between the gross lesions in the larger branches and the histological changes in the smaller branches (arterioles). Often the latter vessels showed no noteworthy changes in the presence of marked arteriosclerosis of the larger branches. In only a few instances did the sections of the myocardium reveal intimal thickening of the arterioles. None of the sections, however, showed changes characteristic of obliterating endarteritis. Occasionally a moderate infiltration of round cells and endothelial cells was found in the perivascular spaces, but in no instance was there evidence of syphilis of the coronary arteries.

In the 32 instances in which thrombi were encountered in the coronary arteries, the thrombi were located on atheromatous ulcers. The sections revealed either recent thrombi which showed no evidence of organization or organizing thrombi with partial replacement by connective tissue. In some sections much calcification was found, while others revealed typical atheromas in the subintimal layers of the coronary arteries.

Location of Coronary Lesions.—In all instances both coronary arteries were involved, but most frequently the more severe lesions were found in the left coronary artery, especially in its descending branch about 2 to 3 cm. from its origin. The next most severely affected branch of the left coronary artery was the ramus anterior ventriculi sinistri. The occluding point was often demonstrated in an area about 1 cm. distal to its mouth. The ramus marginis obtusi was involved eight times. The circumflex branch of the right coronary artery was narrowed in 22 instances and occluded by calcified plaques in only one instance; the more severe lesions were found in an area about 3 cm. distal to its mouth. Thrombi in the coronary arteries were found most frequently where the arteriosclerotic lesions were most marked, namely, in the descending branch of the left coronary artery. Thrombi were found in this artery in 14 instances. The posterior descending branch revealed thrombi in two, and marked arteriosclerotic changes in five instances. It may be mentioned in this connection that in five cases this branch came off the left coronary artery, and in only two of these five instances was it free from changes.

TABLE I

CASE	RIGHT CORONARY ARTERY		LEFT CORONARY ARTERY				HEART	TYPE OF DEATH
	RIGHT CIRCUMFLEX BRANCH	POSTERIOR DESCENDING BRANCH	ANTERIOR DESCENDING BRANCH	LEFT CIRCUMFLEX BRANCH	RAMUS VENTRICULI SINISTRI ANTERIOR	RAMUS MARGINIS OBTUSI		
I	Marked narrowing by calcified plaque	Recent thrombus	Occlusion by calcified plaque					Sudden
II	Almost complete obliteration by calcified plaque		Occlusion by calcified plaque		Almost complete obliteration by calcified plaque		Aneurysm involving apical portion of left ventricle	Sudden
III	Recent thrombus					Occlusion by calcified plaque	Recent infarct in latero-posterior wall of left ventricle	Sudden
IV	Almost complete obliteration by calcified plaque		Recent thrombus		Occlusion by calcified plaques		Recent infarction involving apical portion of l. ventricle	Sudden
V	Organizing thrombus		Recent thrombus (Main stem)					Sudden
VI	Organized thrombus. Marked narrowing by calcified plaque		Recent thrombus	Marked narrowing by calcified plaques				Sudden
VII	Recent thrombus		Marked constriction by calcified plaque		Old occlusion by arteriosclerotic plaques	Old occlusion by arteriosclerotic plaque	Recent infarct in latero-posterior portion close to base	Sudden
VIII	Almost complete obliteration by calcified plaque		Occlusion by calcified plaques		Occlusion by calcified plaques		Recent infarct involving apical portion of l. ventricle	Gradual

TABLE I—CONT'D

IX	Almost complete obliteration by calcified plaque		Recent thrombus		Old occlusion by calcified plaque		Recent infarct involving apical portion of left ventricle	Gradual
X	Narrowing by calcified plaques		Recent thrombus	Narrowing by calcified plaques	Narrowing by calcified plaques		Infarct involving anterior wall of left ventricle	Gradual
XI	Marked sclerosis with narrowing by calcified plaques		Recent thrombus	Almost complete obliteration by calcified plaque			Infarct involving lower half of septum, apex and anterior wall	Gradual
XII	Almost complete obliteration by calcified plaques		Almost complete obliteration by calcified plaque		Almost complete obliteration by calcified plaque		Old infarct with aneurysmal dilation in apex	Sudden
XIII	Almost complete obliteration by calcified plaques		Recent thrombus		Almost complete obliteration by calcified plaque		Recent infarct involving anterior wall of l. ventricle and septum	Gradual
XIV	Almost complete obliteration by calcified plaque	Branch of l. cor. art.	Almost complete obliteration by calcified plaque		Recent thrombus		Recent infarct in lateral wall of left ventricle	Sudden
XV	Recent thrombus			Complete obliteration by calcified plaques			Recent infarct in left ventricle close to base	Gradual
XVI	Marked narrowing by calcified plaque		Organizing thrombus		Marked narrowing by calcified plaque		Old and recent infarcts, apic., port., l. vent., and septum	Gradual
XVII	Narrowing by calcified plaque		Organizing thrombus	Narrowing by calcified plaque				Gradual
XVIII	Recent thrombus	Marked constriction by arteriosclerotic plaques	Marked constriction by arteriosclerotic plaques	Marked constriction by arteriosclerotic plaque			Old infarct, apex and recent infarct, base of l. ventricle	Sudden

TABLE I—CONT'D

CASE	RIGHT CORONARY ARTERY		LEFT CORONARY ARTERY				HEART	TYPE OF DEATH
	RIGHT CIRCUMFLEX BRANCH	POSTERIOR DESCENDING BRANCH	ANTERIOR DESCENDING BRANCH	LEFT CIRCUMFLEX BRANCH	RAMUS VENTRICULI SINISTRI ANTERIOR	RAMUS MARGINIS OBTUSI		
XIX	Marked constriction by calcified plaque			Organized thrombus			Old infarct in left ventricle close to base	Gradual
XX	Almost complete obliteration by calcified plaque			Marked narrowing by calcified plaque		Organized thrombus	Organizing infarct in latero-post. wall of l. ventricle	Sudden
XXI	Marked narrowing by arteriosclerotic plaque	Marked narrowing by arteriosclerotic plaques	Recent thrombus at point of division into these two branches				Recent infarct in apex, rupture and hemopericardium.	Sudden
XXII		Branch of l. cor. art. Marked narrowing by calc. pl.	Almost complete obliteration by calcified plaques	Marked narrowing by calcified plaques			Organizing infarct in latero-post. wall of left ventricle	Gradual
XXIII	Complete obliteration by calcified plaque		Marked narrowing by calcified plaque				Old infarct in apex of left ventricle	Gradual
XXIV	Narrowing by calcified plaque		Organizing thrombus		Obliteration by arteriosclerotic plaques		Organizing infarct in apex of left ventricle	Gradual
XXV		Branch of l. cor. art. Marked narrowing by calc. pl.	Organizing thrombus		Marked narrowing by calcified plaques	Marked narrowing by calcified plaques	Organizing infarct in anterior wall of left ventricle	Sudden

TABLE I—CONT'D

XXVI	Marked narrowing by calcified plaques		Organizing thrombus	Marked narrowing by calcified plaques			Organizing infarct in apex of left ventricle	Gradual
XXVII		Old thrombus	Narrowing by calcified plaques	Narrowing by calcified plaque		Narrowing by calcified plaque	Old infarct (aneurysm) in post. wall of left ventricle	Gradual
XXVIII	Constriction by calcified plaques		Recent thrombus and organized thrombus	Constriction by calcified plaques	Constriction by calcified plaque	Constriction by calcified plaques	Two aneurysms, one in apex, one in base of left ventricle	Sudden
XXIX	Narrowing by calcified plaques	Branch of l. cor. art.	Old thrombus	Recent thrombus	Almost complete obliteration by calcified plaque	Almost complete obliteration by calcified plaque	Organ. infarct in ant. wall at apex, old infarct in lat.-post. base of l. ventricle	Sudden
XXX	Arteriosclerotic plaques		Organizing thrombus	Almost complete obliteration by calcified plaque		Almost complete obliteration by calcified plaque	Organizing infarct with aneurysm in apex of l. ventricle	Sudden
XXXI	Recent thrombus		Complete obliteration by calcified plaque	Narrowing by calcified plaque	Narrowing by calcified plaque		Old infarct with aneurysm in anterior wall of l. ventricle	Sudden
XXXII	Narrowing by calcified plaques	Narrowing by calcified plaques	Marked narrowing by calcified plaques	Marked narrowing by calcified plaques	Marked narrowing by calcified plaques		Old infarct in the anterior walls of r. and l. ventricles	Gradual
XXXIII	Recent thrombus		Marked narrowing by calcified plaques	Marked narrowing by calcified plaques	Old thrombus		Old infarct in the apex of the left ventricle	Sudden
XXXIV	Marked narrowing by arteriosclerotic plaque	Branch of l. cor. art. Almost comp. obl. by calc. pl.	Almost complete obliteration by calcified plaque		Almost complete obliteration by art. scl. plaque		Recent infarct in anterior wall of left ventricle	Gradual

In some instances the thrombus did not cause a sudden occlusion of the lumen, but was at first mural in type. Later, the thrombus apparently increased in size and eventually occluded the lumen. This could be demonstrated in the histological sections by observing an older thrombus close to the wall of the artery at one side, with the more recent thrombus adjacent to it.

Levine and Brown[2] stated that in 39 of their 45 autopsy cases, the infarction of the myocardium was found within the distribution of the descending branch of the left coronary artery. They also noted that when the anterior descending or the circumflex branches of the left coronary artery were the involved vessels, the occlusion was usually found about 2 cm. distal to the bifurcation of these branches. This region was also recognized by Mönckeberg[13] as the seat of the severest changes of the coronary arteries. Kirch[7] referred to this location as "Lieblingsstelle" (place of predilection). It may be said in this connection, however, that other investigators, like Bork[11] and, very recently, Barnes and Ball,[14] do not agree that the left coronary artery is more frequently involved than the right. The latter investigators believe that the designation of the anterior descending branch of the left coronary artery as "the artery of coronary occlusion" is not justifiable. Wolkoff[15] in an extensive study on coronary arteriosclerosis, however, has shown that the left coronary artery is more commonly involved than the right and that the changes are more pronounced in its distal portions. She maintained that the point of division in the smaller branches and, more commonly, those portions of the walls of the vessels which are directly attached to the myocardium are the sites of predilection. This author believes that the arteriosclerotic lesions at branching points are the result of the pressure directed against these areas.

Analysis of our material fails to reveal why the descending branch of the left coronary artery presents the more frequent and severe lesions. We could not demonstrate any single point as the one most commonly involved, but found the involvement confined mostly to an area approximately 1 cm. in length beginning about 2 cm. from the point of origin of the descending branch. This would speak against pressure exerted upon branching points as the cause of arteriosclerosis, because the lesions were not confined to the branching points but occurred in wider areas.

Myocardial Lesions.—Depending upon the relative age of the myocardial lesions, various changes were found. In every instance, however, much fibrosis was present in the myocardium, and was especially noticeable in the perivascular spaces. The connective tissue was usually poor in nuclei, and many of the fibers were hyalinized.

One of the most striking findings in this series of hearts was the fact that whenever a myocardial infarct was encountered, at least two branches of the coronary arteries supplying the infarcted area were involved. In this consecutive series of cases no instance was found in which myocardial infarction occurred with only one main artery involved. The involved branches were either completely occluded by calcified plaques or thrombi, or extremely narrowed by calcified plaques. Where extreme narrowing only was present, at least three main branches were involved.

The infarcted areas in general were present in those regions which were supplied by the diseased branch of the coronary artery. The most common site, therefore, was the apical region of the heart. Sometimes parts of the septum were involved. Less frequently, the posterior wall of the left ventricle showed infarcts. In a few instances infarcts were found in both of these regions. In only one instance was an infarct noted in the anterior wall of the right ventricle. Occasionally a recent thrombus was found in one coronary artery, while the recent infarct was found in an area supplied by the opposite coronary artery. In three instances (Cases III, VII, and XX) the infarcts were found in the lateroposterior wall of the left ventricle close to the base. In Case XX, the supplying branch, the ramus marginis obtusi of the left coronary artery, was occluded by a recent thrombus, and the circumflex branch of the right coronary artery showed an almost complete occlusion by calcified plaques. In Cases III and VII, however, the ramus marginis obtuse was occluded by an old calcified plaque. In each, the infarct, being very recent, could not have been the result of this old occlusion. The circumflex branch of the right coronary artery revealed a recent thrombus. The area, normally supplied by the ramus marginis obtusi, must have been supplied in these instances prior to the recent occlusion by collaterals originating from the right coronary artery. In these two cases, therefore, the thrombus of the circumflex branch of the right coronary artery had caused an infarct in an area which originally was supplied by a branch of the left coronary artery.

In Cases XII, XXII, XXXII, and XXXIV myocardial infarcts were present, but none of the branches of the coronary arteries was occluded, although their lumina were markedly narrowed. The occurrence of these infarcts may be explained by the assumption that prior to the development of the infarcts the heart muscle was temporarily insufficient resulting in a lowering of the arterial blood pressure so that the area could not be adequately supplied with blood. We believe that the infarcts developed as a result of this temporary lack of blood supply.

Sections which were taken from the recent infarctions revealed only bare outlines of muscle fibers which showed a loss of their nuclear staining quality. In many instances, however, the connective tissue nuclei were still recognized, and the walls of the smaller blood vessels had escaped necrosis. In large recent infarcts, however, neither connective tissue nor vessel wall was preserved. Very occasionally, these changes were the only ones which could be found, a reactive process being absent. The first evidence of a reaction of the surrounding tissue to necrosis was a marked hyperemia with capillary enlargement and a moderate extravasation of red blood cells. The hyperemia in some instances was so marked as possibly to justify the term "red infarcts." In smaller infarcts, the hemorrhagic type was more noticeable than in the large ones. The recent infarcts also showed a polymorphonuclear leucocytic reaction; first, surrounding the dead muscle fibers and, later, invading the infarcted areas. In some fields these infiltrations gave the impression of an acute pyogenic inflammation. Wearn[16] has also called attention to such infiltrations. We cannot emphasize too strongly the occurrence of polymorphonuclear leucocytic infiltrations in infarcted regions because their presence in the myocardium in cases of sudden death is sometimes erroneously taken as evidence of so-called "malignant syphilitic myocarditis."

In many sections pigment granules were found either free in the tissue or in the cytoplasm of endothelial cells. The granules gave a positive iron reaction and were taken as evidence of old hemorrhage.

The histological picture of old infarcts is well known. One interesting finding, however, may be especially mentioned. In addition to old areas of fibrosis, large areas were often seen in which outlines of heart muscle fibers were still recognizable even though the fibers seemed to have been replaced by a material resembling old hyaline. Occasionally recent, organizing and healed infarcts were seen in a single section. This was observed more frequently when the infarcts were the result of occlusion of the vessel by arteriosclerotic plaques. These findings seem to indicate that the myocardial lesions, like the lesions in the coronary arteries, were progressive in nature.

It is known that the heart muscle fibers show very little tendency toward regeneration. Kaufmann,[17] however, described attempts at regeneration (Regenerationsanläufe) in the vicinity of myocardial infarcts. Such attempts, he believed, were indicated by the findings of so-called muscle giant cells close to the infarcted portions. It is, of course, questionable whether such giant cells really represent attempts at regeneration, or whether they should be classified as foreign body giant cells, the result of myocardial necrosis. In none of our sections were we able to observe giant cells. The only evidence of a compen-

satory reaction of the myocardium in the vicinity of the infarcted areas was an apparent hypertrophy of muscle fibers.

There were six instances of cardiac aneurysms. The larger aneurysms were bulging, and consisted of thin layers of fibrous tissue ("chronic aneurysms"). The endocardium in the region of the aneurysms was thickened and was often covered by thrombi. In one instance a recent infarct led to rupture and hemopericardium resulted. Occasionally, however, before the heart was opened, circumscribed thin depressed areas were noted, which projected into the ventricular cavity. These areas, obviously aneurysms in respect to their pathogenesis and histological appearance, were inverted at autopsy because of the loss of the positive intraventricular pressure. The endocardium corresponding to these inverted areas was thickened but free from thrombi.

In a number of instances infarcts were found in the left ventricle, which were silent clinically; that is to say, there was no history of attacks of pain or other symptoms suggestive of infarction, nor did cardiac insufficiency develop. This point was stressed very recently by Koch and Kong,[12] who stated that cardiac damage and cardiac insufficiency do not go hand in hand. These authors stated various reasons for the relative harmlessness of infarcts located in the anterior wall of the left ventricle. It might be possible that these regions are "silent" areas. In our series, however, there were three instances of infarcts involving the posterior wall of the left ventricle which also did not reveal clinical symptoms.

Collaterals of the Coronary Arteries.—In our series, several instances were encountered of occlusion of a main branch of the coronary artery either by an arteriosclerotic plaque or by an organized thrombus, but without infarction of the myocardium. This clearly indicates that the regions supplied by the occluded vessel must have received their blood supply from other sources. Gross[10] has shown that there is an increase of collateral anastomoses with advancing age. The age group of our series (forty-five to seventy-six years) justifies the assumption that collateral anastomoses were present which must have supplied the areas deprived of their normal arterial supply.

As to the question whether Thebesian vessels might have prevented the infarctions in some of our hearts, the following might be said: Direct communications between the coronary vessels and the ventricular cavities do exist. It has been recently shown (Bohning, Jochim and Katz[18]) that bismuth and bacteria may enter the coronary system via the Thebesian vessels in the beating heart. It still, however, remains to be proved whether or not these Thebesian vessels can supply the myocardium to any large extent when the coronary arteries are occluded. Though it is well known that a gradual occlu-

sion of one or both openings of the coronary arteries, as seen so often in instances of syphilitic aortitis, may occur without myocardial infarction, it still is possible that there is another entrance to the coronary circulation which has not received enough attention. Langer[19] in 1880 and v. Redwitz[20] in 1909 had pointed out such extracardiac anastomoses. Smetana[21] recently has shown anastomoses between the vasa vasorum of the aorta and the coronary arteries. A widespread extracardiac coronary collateral circulation was described recently by Hudson, Moritz and Wearn.[22] These authors also stated that this collateral circulation is probably of significance in compensating for sclerosis of the large trunks of the coronary arteries. Such arterial communications in cases of gradual occlusion of the coronary arteries may prevent infarctions. Special attention to such anastomoses is being given to autopsy material, the results of which will be published in the future. In our series, the absence of infarctions can be explained solely by existing anastomoses between the coronary arteries. The fact that at least two main branches of the coronary arteries were involved when infarcts were present supports this view.

Type of Death.—An attempt was made to correlate the type of death with the anatomical lesions. The cause of death in three patients who died suddenly was undoubtedly thrombosis of a main branch of one coronary artery, the main branch of the opposite coronary artery having been already occluded by an old arteriosclerotic plaque. Once the recent thrombus was found in the right coronary artery (Case I), while in two instances the recent thrombus was found in the left (Cases V and VI). These patients showed no myocardial infarctions, death having occurred before the infarcts could be established. Such a death must be considered as being the direct result of coronary thrombosis. We have not encountered a single case in this series in which death occurred suddenly as the result of the occlusion of a single main branch. It seems as though in this age group (forty-five to seventy-six years) the closure of a single main branch of the coronary system does not cause instantaneous death provided the other branches are patent. Moreover, as Case XVII reveals, a thrombus in the main branch of one coronary artery does not necessarily lead to an infarct in the heart, presumably because of a well-developed collateral circulation.

In the remaining instances death ensued as a result of myocardial incompetence in the great majority associated with myocardial infarction. Though the infarcts were caused by the lesions of the coronary artery (either thrombosis or arteriosclerotic occlusion), such lesions were not the direct cause of death. These patients survived the coronary occlusion for various lengths of time but died later of the myocardial damage. Since such an impaired myocardium may become

insufficient either gradually or suddenly, the patients with myocardial infarcts may die suddenly or succumb slowly. Sixteen patients of this group succumbed gradually, and fifteen died suddenly. In some instances the final factors which led to a sudden greater demand upon the heart just before death could be deduced. The use of a bedpan, a sudden attempt to leave the bed, or other physical strains (perhaps psychic upsets) must have called for a sudden increase of work of the heart to which the impaired myocardium could not respond and the patient died instantaneously.

Angina Pectoris in the Light of the Anatomical Findings.—Eighteen patients revealed attacks which clinically were typical of angina pectoris. A number of these patients revealed thrombosis of the coronary arteries, arteriosclerotic occlusion of the coronary arteries, and also myocardial infarctions. Yet similar conditions were found in the hearts of patients who neither revealed clinical evidence of angina pectoris nor gave a history of such a syndrome. Moreover, severe arteriosclerosis of the coronary arteries and even myocardial infarctions were found at autopsy in patients who had had no symptoms of heart disease. Therefore, it seems untenable to explain angina pectoris on the basis of coronary thrombosis, coronary sclerosis, or myocardial infarction per se.

A large number of clinicians still explain angina pectoris on the basis of spasm of the coronary arteries and the resulting myocardial ischemia. From the point of view of the morphologist, nothing can be said for or against spasm of the coronary arteries as the cause of angina pectoris because evidence cannot be obtained of the existence of spasm in the gross or histological picture. It seems difficult, however, to understand how a vessel wall, markedly thickened as a result of arteriocleroşis and often presenting calcified walls, could be subjected to temporary spasm. From a morphological point of view we also have no means of evaluating or confirming ischemia as a cause of angina pectoris, although we are aware of the experimental work indicating it as a possible cause.

Büchner[23] recently reported ten patients with angina pectoris who died shortly after their attacks. Autopsies revealed infarcts of the myocardium in every instance, although some of these could be detected only by a microscopical examination. He concluded that these latter infarcts were of importance in considering the anatomical equivalent of angina pectoris. In our material a detailed histological examination of the myocardium from blocks cut from various portions of the hearts failed to disclose evidence of such infarcts in hearts of patients who had had typical attacks of angina pectoris. We feel that sufficient portions of the myocardium were examined in a sufficient number of cases with negative results to rule out the possibility of

minute infarcts having caused every attack of angina pectoris. We do not believe that a myocardial infarct, although minute, is the necessary anatomical equivalent of angina pectoris.

One possible explanation for the attacks of angina pectoris may be constructed from this study. All our cases revealed coronary lesions and resulting myocardial damage. While we cannot believe, as mentioned before, that a rigid coronary artery may be subjected to spastic contractions and resulting ischemia, it might be possible that the damaged heart in these instances develops a temporary insufficiency. In every instance of angina pectoris a damaged myocardium could be demonstrated severe enough to explain a temporary insufficiency. The damage is not necessarily caused by an infarct, but may be caused by simple myocardial fibrosis. The final causes for a temporary myocardial insufficiency may be insignificant. As a result of the insufficiency, the arterial blood pressure is lowered, the heart output is decreased, and the blood supply through the narrowed coronary arteries is interfered with. The momentary decrease of coronary blood supply or its effects, whether ischemia, dilatation of the postcapillary veins or the compensatory adjustment of the heart, etc., may be responsible for angina pectoris.

DISCUSSION OF ELECTROCARDIOGRAMS

Following the work of Herrick,[24] Smith[25, 26, 27] and Pardee,[28, 29] it has been generally accepted that characteristic changes in the electrocardiogram result from recent coronary occlusions. The earliest change is a noticeable deviation of the S-T segment from the isoelectric level. Later the S-T segment becomes isoelectric, shows a residual convexity, and is followed by a pointed T-wave with rounded shoulders and symmetrical limbs. The direction of the T-wave is opposite to the original deviation of the S-T segments. In succeeding records the size of this T-wave waxes and wanes, and eventually the T-wave may disappear. Parkinson and Bedford[30] pointed out that the serial changes in the electrocardiogram, with rare exceptions, can be placed in one of two groups. Early in the first group, the so-called T_1 type, the S-T segment is elevated in Lead I and depressed in Lead III; later the T-wave in Lead I becomes negative. Early in the second group, the so-called T_3 type, the S-T segment is elevated in Lead III and depressed in Lead I; later the T-wave in Lead III becomes inverted. Bohning and Katz[31] have called attention to the development of a large, upright T-wave in Lead III in type T_1 and in Lead I in Type T_3. Recently, Wilson and his coworkers[32] attempted to classify electrocardiograms following coronary occlusion into two groups, depending upon the lead in which a large negative Q-wave appeared. In the Q_1 type this negative Q-wave is found in Lead I, and there may be a large nega-

tive S-wave in Lead III; in the Q_3 type this negative Q-wave is found in Lead III, and a negative S-wave may appear in Lead I. The literature contains instances of recent coronary occlusion where the electrocardiographic findings do not fit into the characteristic Q or T patterns. Furthermore it is not always easy to classify the Q-T type.

Barnes and Whitten[33] concluded that the changes in the electrocardiogram depended upon the location of the infarct. They found that the T_1 type is characteristic of infarction of the anterior wall and apex of the left ventricle, and the T_3 type of infarction of the posterior wall of the left ventricle. This conclusion has been confirmed by several authors (cf. Rose and Meyers,[34] Wood and his associates.[35] However, Gilchrist and Ritchie,[36] after comparing the electrocardiograms with autopsy findings in published cases, concluded that the available evidence does not support the view that the form of the electrocardiographic record is a reliable guide in locating the site of the infarct. Wilson and his coworkers,[32] after surveying their material, state "that the location of the infarct plays a most important rôle in determining the form of the ventricular complex in coronary occlusion is scarcely to be doubted. When an attempt is made, however, to correlate the one with the other . . . . many puzzling cases are met with." They found a number of instances both in their own series and in those reported in the literature where the infarct was not located in the region anticipated from the type of the electrocardiogram. Fenichel and Kugel[37] have suggested that a large inverted Q_3-wave is due to infarction of the posterior portion of the ventricular septum.

Gilchrist and Ritchie[36] pointed out that while rapid changes in the ventricular complex in serial electrocardiograms are strong presumptive evidence of myocardial infarction, similar changes developing over a long period of time may be due to progressive myocardial fibrosis following coronary sclerosis. It is now well recognized that ectopic rhythms, such as premature systoles, paroxysmal tachycardia, paroxysmal auricular fibrillation or flutter and terminal ventricular fibrillation, follow recent coronary occlusions. Partial or complete A-V block and intraventricular block (bundle branch or arborization types) also may follow recent coronary occlusion. Smith[27] and Wearn[16] have found small amplitude of the QRS complexes after a recent coronary occlusion.

Many of the views concerning changes in the electrocardiogram following recent coronary occlusion are based to a large extent on a correlation of the records with the clinical findings alone; no autopsies having been performed to confirm the clinical interpretation. This study, however, has shown, as mentioned above, that lesions expected from the clinical picture are not always found at autopsy. Further-

Table II

Summary of Electrocardiographic Findings

Case	Time EKG taken: Before infarction	Time EKG taken: Soon after infarction	Time EKG taken: Some time after infarction	Does it indicate recent coronary occlusion?	Axis deviation	Block present	Q type	T type	Does it correspond with: Wilson's classification of Q type	Does it correspond with: Barnes and Whitten's classification of T type	Low amplitude present	Ectopic rhythms	Location of infarct when record taken
VII	Yes			No	Left	None	3	3			No	Auricular extra.	None present
VIII 1st	Yes			No	Left	Intraventricular common type bundle	?	?			No	Ventricular extrasystoles	None present
XIII 1st	Yes			Compatible with late stage	Left	None	?	3			No	None	None present
XIV	Yes			Yes	Left	None	3	3			Yes	None	None present
XVII	Yes			No	Left	None	1(?)	?			No	None	None present
XVIII 1st	Yes			No	Left	None	?	?			No	None	None present
XX 1st	Yes			No	None	None	?	3(?)			No	None	None present
XXIV	Yes			Suggestive in view of history	Left	None	1	1			Yes	Sinus tachycardia	None present
XXXIV 1 and 2	Yes			No	Left	None	3	3			No	Auricular fibrillation	None present

TABLE II—CONT'D

XXXIV 3	Yes			Suggestive in view of history	Left	None	3	3			No	Auricular fibrillation	None present
II 2nd			Yes	Suggestive in view of first record	Left	Intraventricular common type bundle	?	3	?	No	No	Nodal rhythm	Anterior apex
XII			Yes	No	None	None	1	?	Yes	?	No	Auricular extrasystoles	Anterior apex and anterior septum
XVIII 3 and 5			Yes	No	Left	None	?	?	?	?	No	Ventricular extrasystoles	Anterior apex
XXVIII			Yes	No—but compatible	None	None	1	?	Yes and No	?	Yes	Ventricular extrasystoles	1. Anterior apex 2. Posterior base
XXX			Yes	No	None	Intraventricular indeterminate	?	?	?	?	No	None	Anterior apex and anterior septum
III		Yes		Suggestive in view of history	Left	Intraventricular common type bundle	3	3	Yes	Yes	No	Auricular fibrillation; ventricular extrasystoles	Posterior base
IV		Yes		No—but compatible in view of history	Right	None	?	?	?	?	Yes	None	Anterior apex and anterior septum

TABLE II—CONT'D

CASE	TIME EKG TAKEN			DOES IT INDICATE RECENT CORONARY OCCLUSION?	AXIS DEVIATION	BLOCK PRESENT	Q TYPE	T TYPE	DOES IT CORRESPOND WITH		LOW AMPLITUDE PRESENT	ECTOPIC RHYTHMS	LOCATION OF INFARCT WHEN RECORD TAKEN
	BEFORE INFARCTION	SOON AFTER INFARCTION	SOME TIME AFTER INFARCTION						WILSON'S CLASSIFICATION OF Q TYPE	BARNES AND WHITTEN'S CLASSIFICATION OF T TYPE			
VIII 2nd		Yes (May have been just before)		Suggestive in view of first *record*	Left	Intraventricular common type bundle 1st degree A-V	3	3	No	No	No	Ventricular extrasystoles	Anterior apex and anterior septum
IX		Yes		No	Left	Intraventricular common type bundle	?	1(?)	?	?	No	Auricular flutter in second record	Anterior apex and anterior septum
XI		Yes		No	Left	None	?	1(?)	?	?	No	Ventricular extrasystoles	Anterior apex and anterior septum
XIII 2 and 7		Yes		Yes—in view of first record	Left	None	1	1(?)	Yes	Yes (?)	No	None	Anterior apex and anterior septum
XVIII 2		Yes		Yes—in view of previous record	Left	None	1	3	Yes	No	No	None	Anterior apex

TABLE II—CONT'D

XVIII 6		Yes	Yes	Yes—in view of previous record	Left	None	?	3	?	Yes	Yes	Ventricular extrasystoles, sinus tachycardia	1. Posterior base (recent) 2. Anterior apex (old)
XX 2 and 3		Yes		Yes—in view of previous record	None	None				Yes	Yes	Sinus tachycardia	Posterior base
XXV		Yes		Yes	None	None	1	3(?)	Yes	No (?)	Yes	None	Anterior apex
XXVI		Yes		Yes—because of change in three records	1st right	Intraventricular uncommon type bundle	3	3	No	No	No	Sinus tachycardia	Anterior apex and anterior septum
XXIX		Yes	Yes	Yes—in view of history	None	Intraventricular arborization type	3	3	No (recent) Yes (old)	No	Yes	Ventricular extrasystoles	1. Anterior apex (recent) 2. Posterior base (old)
II 1st	?	?	?	No	Left	Intraventricular common type bundle	?	3			No	None	Possibly anterior apex
XXIII	?	?	?	No	Left	1st degree A-V block	?	?			No	None	Possibly anterior apex

more, neither coronary thrombosis nor myocardial infarction always gives characteristic clinical evidence. The electrocardiographic findings in the present study, therefore, were correlated with the changes found at necropsy. The apparent duration of the thrombosis or infarction was determined by gross and histological examination. With this information we could determine, with reasonable certainty, whether the electrocardiogram was taken before, shortly after, or some time after, the myocardial infarction (or coronary thrombosis) had occurred. The findings are assembled in Table II. Since the study started at the autopsy table, it was not surprising to find that for a variety of reasons electrocardiograms had not been taken in a number of instances and had not been taken often enough in others.

Of the 34 patients studied, 21 had one or more electrocardiograms. Of these, ten were taken before infarction occurred; five were taken a long time after infarction occurred; twelve were taken soon after infarction. At the time two of the last twelve records were taken an old infarct was present in addition to the recent one. The time relationship between the electrocardiogram and the infarct could not be determined in two other instances.

Electrocardiograms Taken Before Infarction.—The electrocardiograms taken before infarction occurred might be expected to show only the changes caused by advanced coronary sclerosis and myocardial fibrosis. Four of these records, however, either suggested a recent coronary occlusion or at least were compatible with such a lesion (record 1 of Case XIII, Cases XIV and XXIV, and record 3 of Case XXIV). Case XIV is particularly noteworthy in this regard. The record showed a typical early Q_3-T_3 type with low amplitude, but no infarct was present. The record in Case XXIV, and the third record in Case XXXIV not only had suggestive changes in the electrocardiogram but suggestive histories as well, and yet no infarcts were present at the time the records were taken.

Electrocardiograms Taken Some Time After Infarction.—Of the five cases in which the records were taken some time after infarction had occurred, three showed nothing characteristic of such an event. The intraventricular block in the second record of Case II and in the record of Case XXX is not necessarily an indication of infarction, since it also occurs in this series when infarcts were not present (record 1 of Case VIII). Low amplitude which was found once in the presence of infarction is not characteristic, since it was found in Cases XIV and XXIV when no infarcts were present. Premature systoles were also found in Cases VII and VIII before infarction had occurred.

It was not easy to determine the Q-T type in the records taken a long time after infarction had occurred. Two of the five showed a Q_1 type, one associated with an infarct in the anterior wall, the other

with an infarct in both the anterior and the posterior wall of the left ventricle. In the other three instances the Q-type could not be determined; the infarct in each of these involved the anterior wall. The T-type could be determined only once. In this instance the type was T_3, although the infarct was located in the anterior wall of the left ventricle.

Electrocardiograms Taken Soon After Infarction.—According to the age of the infarct as determined from the morphological picture, records (or series of records) were taken in 12 instances soon after the development of the infarct. In two of these (Cases IX and XI) the records were not at all characteristic of recent coronary occlusion. In the other ten cases the records either were characteristic of recent coronary occlusion, or at least suggested such a lesion when correlated with the clinical findings or when compared with the records taken previously.

Intraventricular block of various types was present in Cases III, VIII, IX, XXVI and XXIX; in Case VIII a first degree A-V block was also noted. The nature of the intraventricular block bore no relation to the location of the infarct. Involvement of the anterior portion of interventricular septum occurred without block (Cases XI and XIII), with the uncommon type of bundle-branch block (Case XXVI), and with the common type of bundle-branch block (Cases VIII and IX). Involvement of the posterior wall of the left ventricle was associated with the common type of bundle-branch block in Case III; but in Case XX a similarly located infarct was not associated with intraventricular block. It must be remembered, however, that in many instances the intraventricular block may have been present before the infarct occurred, and might have been due to advanced coronary sclerosis and myocardial fibrosis.

Ectopic rhythms were no more frequent in this group of cases than in the preceding two groups. Low amplitude occurred more frequently in this group (5 out of 12 times) than in the other two groups. Left axis deviation was present in seven of these twelve cases, in three no deviation was found and in two the deviation was to the right. Left axis deviation, however, was also frequently seen in records obviously taken before infarction occurred.

The Q-T type in this group could be classified more often than in the preceding group. A Q_3-type was observed four times, a Q_1-type, three times. In the other five instances the Q-type could not be determined. In four instances the location of the infarct corresponded to the Q-type; in three it did not. In the five in which the Q-type could not be determined, naturally no correlation could be made. A T_3-type occurred in eight instances, in one instance it was not altogether characteristic; a T_1-type occurred three times, but was not

absolutely characteristic in any. In one record the T-type could not be determined. The location of the infarct corresponded to the T-type localization of Barnes and Whitten in four cases; in five it did not. In three instances no correlation could be made. A deep negative Q_3 was found in this series when the infarct was located in the anterior as in the posterior wall of the septum. This does not agree with the conception of Fenichel and Kugel.[37]

Interpretation of the Electrocardiographic Findings.—This study indicates that the electrocardiogram, so far as the standard three leads are concerned, does not always aid in determining whether or not coronary thrombosis or myocardial infarction is present. The electrocardiogram also does not always aid in estimating the age of the infarct. It is, of course, possible that more information might be obtained if more frequent electrocardiograms are taken and the records compared. The advantage of taking records early in middle life to serve as "controls" for subsequent records is obvious. Such "control" records were of considerable value in six instances in this series. The electrocardiographic changes generally assumed to be due to recent myocardial infarcts may also occur in instances of old infarcts or where no infarct is present. These observations suggest that the characteristic electrocardiographic changes supposedly due to recent myocardial infarcts may be produced by some other factor, such as myocardial ischemia brought on by sudden myocardial insufficiency or by sudden reduction in the force necessary to drive blood through the narrowed coronary arteries. In other words, interference with the coronary blood supply in hearts with marked sclerosis and gradual narrowing of the lumina of the coronary arteries may cause changes in the electrocardiogram which are similar to (or nearly similar to) those produced by thrombosis and infarction. Hence the electrocardiogram may be misleading if reliance is placed entirely on it.

This study further shows that so far as single standard lead records (and even occasionally where serial records are available) the electrocardiogram (1) may fail to show changes considered characteristic of recent infarction when an infarct is present; (2) may show changes compatible with infarction when none is present; (3) may show changes characteristic of recent infarction in the presence of an old infarct; (4) may show changes suggestive of an old infarct in the presence of a recent one; and (5) may show changes commonly produced by coronary sclerosis and myocardial fibrosis in the presence of old healed infarcts. Therefore, the electrocardiogram may entirely fail to give any clues as to the full significance of previous clinical attacks.

Furthermore, we believe that it is not feasible to locate the position of the infarct from records obtained with the standard three leads. If it is assumed that the location of the infarct determines electro-

cardiographic types, this study shows that there must be other factors which modify the appearance of the records (cf. Korey and Katz[38]). Perhaps, as Wilson and his associates[32] suggested, the character of the electrocardiogram may depend to some extent on the location of the infarct with reference to the endocardial and epicardial surfaces of the heart. It is also possible that the condition of the myocardium and the position of the heart prior to infarction may play an important rôle (cf. Katz and Ackerman[39]). While it is of interest to attempt to classify the electrocardiograms into various T- and Q-types, one should not become so engrossed in this endeavor as to lose sight of the fact that many records cannot be so classified. It is more important to take serial records at frequent intervals in suspected cases and to examine the records for minor changes, especially in the contour and level of the S-T segment and contour and direction of the T-wave. If this is done, recent coronary thrombosis and myocardial infarction will be overlooked in fewer cases, although the error of diagnosing infarction and thrombosis when they are not present may still occur when the coronary arteries are markedly sclerosed. The recent work of Wolferth and Wood,[40, 41, 35] of Wilson and his associates[32] and of Katz and Kissin[42] indicates that the frequency with which myocardial infarction can be diagnosed is increased by taking a fourth lead from the chest in addition to the standard three leads.

The variability of the electrocardiograms taken when infarcts were not present suggests that the electrocardiographic changes seen in coronary sclerosis are not due to the fibrous replacement of the heart muscle—unless there is serious interference with the conduction pathways—but are expressions of the damage to the apparently normal muscle resulting from a diminished blood supply of the whole heart which the diffuse arteriosclerotic process in the coronary arteries may produce.

DISCUSSION OF CLINICAL FINDINGS

From the clinical standpoint the method of this study has some disadvantages. Thus is may be argued that some of the patients were not sufficiently studied from the cardiac angle. It is, however, unlikely that significant symptoms or signs were overlooked, particularly attacks suggestive of angina pectoris and congestive heart failure. On the other hand, from the clinical standpoint this approach has the distinct advantage of presenting a group of patients which more nearly represents the average likely to be encountered by the profession at large, rather than a group selected by the specialist in internal medicine. As has been seen from the case reports, a large percentage of the patients sought relief from conditions which were primarily surgical, medical or neurological with cardiac symptoms either absent or occupying a minor place.

Incidence and Associated Lesions.—Before reviewing the points bearing directly upon the clinical picture of coronary thrombosis and myocardial infarction, a brief discussion of the incidence and associated lesions is given in Table III.

TABLE III

A. Incidence:

Sex: Males, 28; females, 6.

Age: 45 to 76 years (majority between 61 and 70).

B. Associated lesions:

1. Generalized arteriosclerosis: 34 (moderate, 18; severe, 16).
2. Nephrosclerosis of the arteriolar variety, 9.
3. Hypertension, 13.
4. Pulmonary lesions:

    Infarcts, 9.
    Embolism of pulmonary artery without infarction, 1.
    Bronchopneumonia, 5.
    Abscess, 1.
    Chronic caseous or fibrous tuberculosis, 4.

5. Lesions in the gastrointestinal tract (including the gallbladder and liver):

    Carcinoma, 5.
    Polyposis, 2.
    Intestinal obstruction, 1.
    Diverticulitis, 1.
    Cholelithiasis, 2.
    Cholecystitis, 2.
    Laennec cirrhosis, 1.

6. Infarcts in organs other than the heart or lung, 10.
7. Glandular hyperplasia of the prostate, 6.
8. Encephalomalacia, 4.
9. Diabetes mellitus, 4.

The presence of generalized arteriosclerosis in every patient is not surprising. Only 13 had evidence of hypertension clinically; some cases may, however, have been overlooked. With the exception of infarcts in other organs and possibly carcinomas, the incidence of other than cardiac lesions is about what might be expected in this age group. Associated lesions assume importance in the clinical consideration of coronary disease when they mask or confuse cardiac symptoms, increase the work of the heart, require surgical intervention, or divert the attention from the heart with the result that this organ is not carefully examined.

Pulmonary Lesions.—Bronchopneumonia occurred chiefly as a terminal event. In at least one instance, however, it precipitated the terminal failure. In another instance the symptoms and some of the findings of bronchopneumonia were interpreted as those of coronary thrombosis. Pulmonary infarction was usually secondary to the cardiac mural thrombi, but in at least one instance the symptoms were interpreted as those of coronary thrombosis. In another instance the presence of pulmonary infarction cast doubt on the existence of coro-

nary thrombosis and led to the explanation of the symptoms and findings on the basis of the pulmonary lesion alone (cf. Hamburger and Saphir[43]). It must be borne in mind, however, that pulmonary infarction should lead to the suspicion of the occurrence of recent myocardial infarction unless another cause is demonstrable. Of the nine instances of pulmonary infarction in this study seven resulted from emboli arising from mural thrombi of the right auricle and only two from emboli originating in the right ventricle. In addition there was one instance of a mural thrombus of the right auricle without pulmonary infarction. Pulmonary infarction following myocardial infarction does not necessarily indicate that the myocardial infarct is located in the interventricular septum adjacent to the right ventricular cavity. It may rather indicate myocardial insufficiency, cardiac dilatation, and consequent auricular thrombi.

Abdominal Lesions.—Some of the abdominal lesions in this group of patients were found incidentally at autopsy. Most of them were recognized clinically while the coronary and myocardial disease was overlooked. With one exception they led to surgical intervention. While it is possible in one or two instances that some of the abdominal symptoms were produced by the coronary disease, the cardiac complication in the other instances was overlooked mainly because the coronary occlusion or thrombosis, or myocardial infarction was clinically "silent." It so happens that the error of operating on a patient with coronary thrombosis in the absence of an abdominal lesion was not made in this particular series. The incidence of carcinoma (all of the gastrointestinal tract) is rather high (15 per cent). It is well known today that the pain of coronary thrombosis may appear only in the upper abdomen (Levine and Tranter,[44] Hamburger[45]). This has been emphasized so much that we are in danger of forgetting that an elderly, arteriosclerotic individual can have abdominal pain resulting from an abdominal lesion even though other symptoms might point to the heart. Errors in diagnosis either way are unfortunate and should be studiously avoided.

Infarcts in Other Organs.—In one instance a renal infarct was mis taken for coronary thrombosis; in another a splenic infarct was diagnosed coronary thrombosis. Other instances of infarcts were clinically not misleading. In one instance, however, hemiplegia following cerebral embolism diverted attention from the heart.

Diabetes Mellitus.—Four patients had diabetes mellitus. This incidence is less than some observers report (Levine and Brown,[2] Nathanson[46]). If the patients comprising this series represent, as we believe, the averages which one might encounter, it follows that diabetes mellitus is not so frequently present as may be inferred from the recent literature.

referable to the heart. In nine of these patients the attacks occurred only after effort (Heberden's angina); in four pain occurred unrelated to effort; the remaining five had both types of pain attacks.

In the group with definite Heberden's angina (fourteen patients altogether) it was impossible to tell in many instances which attacks or which type of pain coincided with coronary thrombosis or myocardial infarction. In three instances (Cases XVIII, XIX and XXVIII) the evidence is reasonably clear that angina of effort developed following the coronary thrombosis or myocardial infarction. The occurrence of pain unrelated to effort has been given as a differential diagnostic point in determining the occurrence of coronary thrombosis. There were only four instances in which an attack of pain unrelated to effort could reasonably be correlated with the occurrence of coronary thrombosis or myocardial infarction. Coronary sclerosis and myocardial fibrosis alone were present in four instances at the time attacks of pain unrelated to effort occurred, showing that in the presence of these lesions obvious exertion is not a prerequisite for the production of pain.

Localization of pain outside the cardiac area was most frequent in the attacks unrelated to effort. In four instances pain was felt solely in the epigastrium, one attack being associated with nausea and vomiting. It has also been said that epigastric localization of pain favors the diagnosis of coronary thrombosis. Of five attacks of pain unrelated to effort and with epigastric localization, three did not signalize coronary thrombosis. In the group with Heberden's angina (fourteen patients altogether) pain occurred in the epigastrium in one instance and in the face and neck in another in addition to being substernal.

In two instances correlation between the attacks of pain and the anatomical findings was not possible because of multiplicity of lesions.

In addition to the eighteen patients discussed above, three other patients had attacks of epigastric or abdominal pain not related to effort and which could not be ascribed definitely to cardiac lesions. In one of these patients (Case VIII) old coronary sclerosis or occlusions might have caused the attacks of epigastric pain, although an infarct of the spleen was also present. In the second (Case XV) there was abdominal pain about the time of coronary thrombosis, but the patient also had carcinoma of the stomach. In the third (Case XVII) an attack of right upper quadrant pain was possibly caused by coronary thrombosis but clinically was more typical of gallbladder disease.

Duration of pain is not a reliable differential diagnostic point in determining the occurrence of coronary thrombosis because of the frequent occurrence of attacks of pain lasting for hours which did not signalize coronary thrombosis. There are no clear-cut instances in our series of short attacks of pain signalizing coronary thrombosis or myocardial infarction.

Severity of pain also is not a reliable guide in the differential diagnosis of coronary thrombosis, since there were attacks of pain, unrelieved by nitrites or morphine, not associated with the occurrence of coronary thrombosis. On the other hand, some comparatively mild attacks of pain signalized coronary thrombosis. Some of the variability in the severity of pain encountered may be explained, in part at least, by variability in the sensitivity of the individual to painful stimuli, a subject which has been emphasized recently by Libman[49] who divides patients into hypo- and hypersensitive groups.

It is interesting to note that thirteen patients did not give a history of any cardiac pain. This group constitutes 38 per cent of the total number of patients in this study and includes those with various types of anatomical lesions, namely, recent coronary thrombosis without myocardial infarction—2 instances, recent coronary thrombosis with myocardial infarction—4, recent myocardial infarction without coronary thrombosis—2, old sclerotic coronary occlusion—1, old coronary thrombosis—1, old coronary thrombosis with myocardial infarction—2, and old myocardial infarction without coronary thrombosis—3. Some hearts had lesions which developed at different times, accounting for the overlapping (Cases XVI, XXXI, XXXII, XXXIII). Every one of these thirteen hearts, however, showed coronary sclerosis and myocardial fibrosis. Congestive heart failure, debilitating disease, or clouded sensorium may explain the absence of pain in a few of these thirteen patients but not in the majority. It may be emphasized that some of these "silent coronary accidents" occurred while the patients were under daily observation in the hospital.

Other Signs and Symptoms.—In looking for other possible clinical signs of coronary thrombosis or myocardial infarction in the group of patients without pain, it was noted that five had an attack of sudden dyspnea related to the development of coronary thrombosis. These sudden attacks of dyspnea were not always accompanied by pallor, fall in arterial blood pressure, fever and leucocytosis. It seems justifiable, therefore, to emphasize the fact that sudden dyspnea may be the only clinical sign of coronary thrombosis. In one instance in the group of patients without pain an attack of faintness was apparently the only significant sign of coronary thrombosis.

Aside from pain and sudden dyspnea, the following summary may be given concerning the remaining symptoms and signs considered characteristic of coronary thrombosis and myocardial infarction. Myocardial infarction was usually associated with fever, although in three instances it was not. In every instance of recent infarction in which a white blood cell count was made, a leucocytosis was found. When previous blood pressure readings were available as controls, a fall in arterial pressure coinciding with coronary thrombosis was usually

noted. But in at least four patients (Cases II, VII, XI and XXVI), the arterial pressure was well maintained or actually rose. Recent or organizing pericarditis occurred nine times, and in four of these instances a friction rub was heard. The friction rub does not indicate that the infarct is located anteriorly, since in two of these four the infarct was found in the posterior wall of the left ventricle. The pulse was usually rapid and of poor quality. Hyperpnea of varying degrees and occasionally dyspnea occurred immediately following coronary thrombosis whether pain was present or not. Pallor, sweating, and weakness were inconstant.

In view of all the facts presented in this discussion it appears impossible in the present status of our knowledge to differentiate clinically between myocardial infarction brought about by coronary thrombosis and that following arteriosclerotic narrowing or occlusion of the coronary arteries. This study also emphasizes the great difficulty of determining clinically the occurrence of coronary thrombosis and myocardial infarction, either because the thrombosis and infarct may occur "silently" or because the characteristic picture may be found in the absence of thrombosis and infarction.

SUMMARY AND CONCLUSIONS

The material of this study comprises thirty-four cases selected by the pathologist on the basis of the anatomical lesions, without previous knowledge of the clinical and electrocardiographic findings. After the anatomical material had been studied, the clinical and electrocardiographic records were reviewed, and the attempt was made to correlate these findings with the anatomical lesions.

Both coronary arteries were involved in all hearts examined. The more severe lesions were found in the left coronary artery, especially in the descending branch. Whenever a myocardial infarct was encountered, at least two branches of the coronary arteries supplying the infarcted areas were involved. The infarcted areas in general were present in the regions supplied by the diseased coronary arteries. Occasionally, a recent thrombus was found in one coronary artery, while the recent infarct was located in an area supplied by the previously occluded opposite coronary artery. Apparently the infarcted area, prior to infarction, was supplied by collateral anastomoses. In four hearts, infarcts were present without any occlusion of the coronary arteries, although their lumina were markedly narrowed. Such infarcts were probably caused by transient myocardial insufficiency, which in the presence of narrowed coronary arteries led to a temporarily inadequate blood flow. Some degree of myocardial fibrosis was present in all hearts.

Patients with myocardial infarcts may die suddenly or succumb slowly. In some instances the final factors, which led to a sudden

greater demand upon the heart just before death, could be deduced. In the great majority of patients, death ensued because of myocardial incompetence associated with myocardial infarction. Sudden death following the occlusion of a single main branch of the coronary arteries was not encountered. Three patients dying suddenly showed recent thrombi in a main branch of one coronary artery, the opposite artery showing an old occlusion.

As far as single standard lead records are concerned (and even occasionally where serial records are available) the electrocardiogram may fail to give any clue as to the full significance of previous clinical attacks. It does not always aid in determining whether or not coronary thrombosis or myocardial infarction is present. The electrocardiographic changes supposedly characteristic of recent myocardial infarcts may be caused by some other factor such as myocardial ischemia brought about by sudden myocardial insufficiency or by sudden reduction in the force necessary to drive blood through the narrowed coronary arteries.

The attempt to locate the position of the infarct from records obtained with the standard three leads is not feasible. If it is assumed that the location of the infarct determines electrocardiographic types, this study shows that there must be other factors which modify the contour of the electrocardiograms.

The variability of the electrocardiograms taken when infarction was not present suggests that the changes seen in coronary sclerosis and myocardial fibrosis are not due to the fibrous replacement—unless there is serious interference with the conduction pathways—but are evidence of damage to the intact myocardium accompanying the lessened blood supply through the arteriosclerotic coronary arteries.

Pain definitely or reasonably referable to the heart occurred in 18 of the 34 patients. There were only four instances in which an attack of pain unrelated to effort could reasonably be correlated with the occurrence of coronary thrombosis or myocardial infarction, yet coronary thrombosis was encountered 32 times. On the other hand, coronary sclerosis and myocardial fibrosis alone were present in four instances at the time attacks of pain unrelated to obvious effort occurred. The duration and severity of pain were found to be unreliable guides in diagnosing coronary thrombosis and myocardial infarction.

Thirteen of these 34 patients did not give any history of cardiac pain. Congestive heart failure, debilitating disease, or clouded sensorium may explain the absence of pain in a few of these patients but not in the majority. Some of the so-called "silent" coronary accidents occurred while the patients were in the hospital. Sudden dyspnea may be the only clinical sign of coronary thrombosis.

Myocardial infarction was usually associated with fever, although in three instances it was not. In every instance of recent infarction in which a white blood cell count was made, leucocytosis was found. When previous blood pressure readings were available as controls, a fall in arterial pressure coinciding with coronary thrombosis was usually noted; but in at least four patients the arterial pressure was well maintained or actually rose. Recent or organizing pericarditis occurred nine times, but a friction rub was heard in only four instances. The friction rub does not indicate that the infarct is located anteriorly, since in two of these four the infarct was found in the posterior ventricular wall. The pulse was usually rapid and of poor quality. Hyperpnea of varying degrees, occasionally dyspnea, occurred immediately following coronary thrombosis whether or not pain was present. Pallor, sweating, and weakness were inconstant signs.

Pulmonary infarction following myocardial infarction may be due to emboli from mural thrombi of the right auricle or right ventricle. The incidence of carcinoma of the gastrointestinal tract was rather high (15 per cent). Diabetes mellitus in our series was not so frequently present as might be inferred from the recent literature. The fact that the pain of coronary thrombosis may appear only in the upper abdomen has been emphasized so much that there is danger of overlooking abdominal lesions.

Anesthesia and surgical procedures may precipitate coronary thrombosis or conditions leading directly to death. The cardiac status of patients in the fourth decade or later, upon whom operation is contemplated, should therefore be carefully evaluated.

Not coronary thrombosis nor myocardial infarction nor coronary arteriosclerotic occlusion can be the anatomical equivalent of angina pectoris because these lesions were found not only in the presence of angina pectoris but also in patients who never had attacks of angina pectoris. Besides, these lesions were not constantly present in hearts of patients dying following attacks of angina pectoris. Only one anatomical change was common to all hearts of patients who had attacks of angina pectoris, namely, coronary sclerosis and myocardial fibrosis. To the morphologist, coronary sclerosis and fibrosis of the heart mean a labile myocardium which may fail suddenly. It seems that the sudden failure, or the subsequent events, is intricately linked with anginal attack in some manner as yet undetermined.

In the present state of our knowledge, it appears impossible to differentiate clinically between myocardial infarction brought about by coronary thrombosis and that following arteriosclerotic narrowing or occlusion of the coronary arteries. It is also difficult to determine the occurrence of coronary thrombosis and myocardial infarction clini-

cally, either because the thrombosis and infarct may occur "silently," or because the characteristic picture may be found in the absence of thrombosis and infarction.

We are indebted to the staff of Michael Reese Hospital for the privilege of studying the clinical records of some of these patients.

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THE HEART IN TYPHOID FEVER

A Clinical Study of 30 Patients*

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Opportunities for studying the cardiovascular system during the course of typhoid fever have been greatly lessened during recent years, so that little data based upon modern concepts of circulatory disease have been accumulated.

The most comprehensive study is that made by Brow[1] during an epidemic of typhoid fever in 1929. He studied sixty-five patients and found that 21.5 per cent showed abnormal electrocardiograms at some periods of the disease. Prolongation of the P-R interval was found in fourteen cases varying in extent from 0.21 sec. to 0.28 sec. The earliest change was noted on the eleventh day and the latest upon the forty-third day of the disease. Only two patients showed T-wave changes. A careful physical examination of the heart during the course of the disease failed to show any evidence indicating heart failure or involvement of the myocardium.

From 1923 to 1933, inclusive, 175 patients ill of typhoid fever have been treated on our medical service. During the past four years we have selected thirty for special cardiovascular studies. Of these, twenty-nine gave no history or physical evidence of previous circulatory disease, and one patient with a history of two attacks of rheumatic fever had the physical phenomena of mitral stenosis.

The routine adopted during this study consisted of daily blood pressure estimations, electrocardiograms once a week, with repetition every third day if changes were found, a daily clinical study of the cardiovascular system, noting particularly phenomena indicative of heart failure of the congestive type, arrhythmias, murmurs, quality of the first cardiac sound, and cardiac size.

The treatment emphasized a high caloric diet, allowing 60 calories per kilogram of body weight. Its composition was protein, 2 gm.; carbohydrates, 5 gm.; and at least 50 c.c. of fluids per kilogram of body weight. No drugs were prescribed except simple remedies to control delirium, cough, diarrhea, and restlessness. No remedies which affect the heart or vascular system were prescribed.

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TABLE I

THE SIGNIFICANT ELECTROCARDIOGRAPHIC DEVIATIONS FROM THE NORMAL FOUND AMONG THE THIRTY PATIENTS STUDIED

CASE	AGE	PULSE RATE*	AVERAGE BLOOD PRESSURE†	ELECTROCARDIOGRAM			REMARKS
1. H. M.	16	79	104/54	P-R	interval 0.21 sec.	25th day	Recovery
2. K. J.	15	88	112/68	P-R	interval 0.23 sec.	24th day	Recovery
3. P. C.	18	87	102/48	T inverted	Lead I	23rd day	Recovery
4. D. C.	20	94	118/59	P-R	interval 0.26 sec.	27th day	Recovery
5. J. R.	17	107	94/54	P-R	interval 0.24 sec.	15th day	Recovery
6. S. H.	19	106	102/62	P-R	interval 0.26 sec.	13th day	Recovery
7. K. G.	17	100	112/74	T isoelectric	Lead I		
				T inverted	Lead II, III	44th day	Recovery
8. F. B.	27	88	102/57	P-R	interval 0.28 sec.	12th day	Recovery
9. L. S.	40	116	100/64	P-R	interval 0.22 sec.	21st day	Death
							Perforation
10. G. P.	19	71	101/62	P-R	interval 0.24 sec.	28th day	Recovery
11. E. R.	32	107	118/55	T inverted	Lead II, III	31st day	Recovery
							Relapse
12. C. H.	21	100	104/52	T inverted	Lead I, II	15th day	Recovery
13. L. J.	30	115	94/46	T diphasic	Lead I, II		
				QRS slurred	interval 0.12 sec.	9th day	Recovery
14. E. F.	24	105	98/47	P-R	interval 0.26 sec.	18th day	Recovery

*Rate recorded with first abnormal electrocardiogram.
†The average systolic and diastolic pressures from daily records.

Table I gives a summary of the pulse rate, average blood pressure, and the significant electrocardiographic deviations from the normal in those patients showing abnormal electrocardiograms.

DISCUSSION

Electrocardiograms.—Forty-six per cent of the patients showed significant changes in the electrocardiogram. The earliest change noted was on the ninth day, and the latest on the forty-fourth day. It is significant that the disturbances observed in the electrocardiograms continued in most instances for a brief period, lasting in only two instances longer than six days. In every patient the electrocardiograms eventually became normal. In not a single patient was there any disturbance of cardiac rhythm except a moderate degree of sinus arrhythmia observed in an occasional patient during convalescence.

Lewis[2] states that conduction defects occur only in the severe types of infection. In our series there was no noticeable difference in the frequency of electrocardiographic changes in those with clinically severe infections and in those with mild infections.

Chagras[3] observed that inversion and diphasic T-waves were the most frequent alteration in the electrocardiograms.

Our findings are in accord with those of Hyman[4] and of Brow, who both noted prolongation of the P-R interval as the most frequent disturbance of cardiac mechanism.

Cardiac Murmurs.—One patient on admission had the physical phenomena of mitral stenosis. He gave a definite history of two attacks of rheumatic fever, at the ages of fourteen and nineteen years. No additional changes were noted in the physical phenomena or electrocardiograms during the course of a very severe typhoid infection. Only two other patients showed murmurs during the course of their illness. These two patients had repeated intestinal hemorrhage with the consequent development of severe grades of secondary anemia. The murmurs were systolic in time, heard both at the apex and over the base of the heart. At the time the murmurs were heard, the hemoglobin was 46 per cent in one patient and 39 per cent in the other. Following transfusions with a partial relief of anemia, the murmurs disappeared. No endocardial or pericardial murmurs were heard in any of the patients, indicating that neither pericarditis nor endocarditis developed to a degree sufficiently significant to produce the usual phenomena of these conditions.

Heart Size.—Special effort was made to determine whether cardiac dilatation occurred during the course of typhoid fever. Reliance was placed principally on the position and character of cardiac apex in determining heart size; nevertheless, in ten of the patients seven-foot x-ray plates were used. In only one patient was there any evidence of conclusive character indicating that cardiac dilatation had occurred. In

this patient, in whom repeated intestinal hemorrhage occurred, there was an excursion of 1.5 cm. of the left border of the heart to the left. In none of the remaining twenty-nine patients could there be demonstrated phenomena indicating that there was a material change in the size of the heart. This statement is applicable both to those who showed changes in the electrocardiograms and to those who had normal electrocardiograms.

Heart Sounds.—The first heart sounds in typhoid fever are notably weak in quality. Frequently in this study the heart sounds were recorded as being short in duration and muffled or distant in quality. While this phenomenon is observed in practically all patients during the active stage of typhoid fever, its significance is difficult of interpretation. It might be interpreted as meaning that heart muscle pathology existed, yet this supposition was not substantiated by cardinal phenomena of congestive heart failure, and a gallop rhythm was never observed. The second sounds were not significantly altered except in two patients. In these two it was noted that the intensity of the second pulmonic sound was increased.

Blood Pressure.—As has been previously observed the blood pressure has been relatively low in all of the patients studied. This is true of both the systolic and diastolic pressures. After the occurrence of intestinal hemorrhage, there frequently follows a critical fall in both the systolic and diastolic blood pressures. This is a more sensitive index of the occurrence of hemorrhage than the rectal temperature, for we have frequently observed blood pressure changes with no significant temperature alterations.

Heart Failure.—In a review of 175 patients who had typhoid fever, thirty of whom are included in this study, not a single patient has shown the phenomena characteristic of congestive heart failure. This is significant for Marris[5] observed high venous pressures in typhoid patients. In none of the patients in this series was there clinical or instrumental evidence of general venous hypertension. Occasionally moderate distention of the veins of the neck occurs in those patients who have marked degrees of tympanitis, yet the venous distention disappears with relief of abdominal distention.

Pulmonary edema associated with left ventricular failure did not occur in a single patient except as a terminal event in those who were dying from complications, such as typhoid perforation. It would be reasonable to expect ventricular failure in patients in whom toxic degeneration of the heart muscle is apparently a rather common complication; yet, from a study of this series, it appears as if an inhibiting factor prevented such serious disturbances of heart muscle function.

SUMMARY AND CONCLUSIONS

1. Of the thirty patients, 46.6 per cent showed significant changes in the electrocardiograms, although the changes were transient in nature. The fact that evidences of cardiac dilatation and heart failure were strikingly absent suggests that the pathological changes which were responsible for the electrocardiographic alterations were either mild in degree or were localized.

2. No disturbances of rhythm occurred; a gallop rhythm was not observed; and there was a notable absence of the phenomena of congestive failure.

3. From a clinical viewpoint the heart presents no significant problem in the treatment of typhoid fever.

4. A study of the literature dealing with typhoid fever prior to the use of high caloric diets indicates that the toxemia of the disease was much greater and serious cardiovascular complications were common. Comparing the recent studies of Brow and the studies herein reported with former studies,[6] one ventures the conclusion that the reduction in the serious circulatory complications may be attributed to the character of the diet now employed in the care of typhoid patients.

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ON THE USE OF CHEST LEADS IN CLINICAL ELECTROCARDIOGRAPHY

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SINCE the introduction of Lead IV by Wolferth and Wood in January, 1932,[1] the use of chest leads has become popular as a routine procedure in clinical electrocardiography. It has stimulated an interest which led cardiographers and clinicians to make further search for leads that might disclose evidences of myocardial damage not readily discernible in the standard leads originally adopted by Einthoven. Consequently various combinations of chest electrodes, or combinations of one chest and one limb electrode, have been employed to "improve" on Lead IV. Some have advocated multiple combinations or hook-ups, advancing the contention that when Lead IV fails, some other chest lead of the group may serve. Nevertheless, up to date, Lead IV still holds sway.

By this lead is meant a combination of two chest electrodes, one anterior and one posterior. The right arm electrode is applied to the immediate vicinity of the cardiac apex, and the left arm electrode* is applied to the dorsum—slightly above and slightly medial to the angle of the left scapula. Tracings derived by this lead, it has been claimed, disclose evidences of myocardial involvement at times when they are not readily seen in the standard leads. For the normal tracing recorded by this lead, Wolferth and Wood presented criteria essentially as follows: The P-wave is negative and small; the QRS is large, diphasic, and its initial deflection is negative; the T-wave is large, negative and is preceded by only a very short isoelectric period. The outstanding feature of this tracing is a magnification of the entire ventricular complex with an inversion of its principal components.

Obviously then, abnormalities in Lead IV are manifested by alterations in the ventricular complex. A shallow or upright T-wave or an absence of the initial negative deflection in the QRS complex would constitute abnormalities in Lead IV. A deviation of the RS-T segment in Lead IV has the same clinical significance as in the standard leads.

To Lead IV, Wolferth and Wood soon added Leads V and VI. This simply meant additional combinations between the two chest electrodes mentioned and the left foot; Lead V recording the potential difference between the *apex* electrode and *left foot;* and Lead VI, the potential difference between the *dorsal* electrode and *left foot*. For reasons to be

*Right arm electrode and left arm electrode refer to electrodes situated anywhere on the body surface, so long as they are attached to lead cables which in standard electrocardiography are connected with the right arm and left arm respectively. For brevity, such electrodes will be designated in this article merely as the R and L electrode.

explained later, Lead V is essentially of the same configuration as Lead IV, and in the light of our present knowledge Lead VI is of no particular value because it yields small deflections, generally smaller than any of the standard leads.

The presentation of Lead IV as an aid in clinical electrocardiography came to us at a time when it was felt by many that the use of the electrocardiogram had nearly reached the height of its potentiality as a diagnostic aid. It came at a time when we were much puzzled by minor changes in the ventricular portion of the electrocardiogram. The prospect of solving them seemed remote, and this, in spite of our having entered the fourth decade of electrocardiography.

The normal electrocardiogram had been deciphered in great detail by the old masters over thirty years ago. Common deviations from normal, as found in disorders of cardiac rate and rhythm, have been presented repeatedly, and their meaning has been clarified. Abnormalities in the auricular P-wave indicating anatomical or physiological changes in the auricles have become common knowledge. Some twenty years ago certain changes in the initial ventricular complex (QRS) had been described, leading to inferences as to types of defect in intraventricular conduction. About ten years ago we had added valuable information as to the meaning of gross changes in the terminal portion of the ventricular complex (R-T and T) in estimating the degree and locating the site of damage in the ventricular myocardium, due to coronary occlusion. Subsequently our knowledge was extended to include the meaning of similar R-T and T changes in other conditions producing localized impairment in myocardial function, as in the pericarditides, inflammatory, neoplastic, and traumatic lesions of the myocardium. The names of the workers who have made these valuable contributions, decade by decade, need not be mentioned here. They are recorded in all modern texts dealing with the elements of electrocardiography.

In the foregoing it has been our object to emphasize, in an approximately chronological order, the gradual, slow rate of accumulation and the subsequent sum total of our knowledge in electrocardiography when Lead IV was introduced. In this connection it should be stressed that when this special lead was introduced, we were preoccupied principally with the study of T-waves and R-T changes as possible indications of myocardial damage and that in the study of these we have been able to interpret the meaning of gross changes only. Minor variations in the terminal phase of the electrocardiogram have been meaningless and are, in a measure, meaningless today. Experiments on hearts of animals have not been productive of information beyond the localization of gross lesions, "anterior" or "posterior" surface lesions. Electrocardiography was in a state of apparent standstill or, at best, at a stage of very slow progress. It was at this time that Lead IV was offered as a further means of information, and, naturally, the subject was received with a

great deal of enthusiasm. The literature that followed with intentions to confirm and presumably to elaborate on the usefulness of Lead IV, reflected this enthusiasm unmistakably. Some of the earlier literature seems to have been colored by it as if expressing a wish that chest leads would do what the standard leads could not do.

Several articles appeared in the literature in rapid succession, confirming the "criteria" for Lead IV, and endorsing its adoption as a part of routine electrocardiography. These articles appeared at a time when the originators of Lead IV seemingly had not as yet crystallized their own ideas as to the value of chest leads as a clinical routine. They were still in the early experimental stage of their work. As their subsequent articles will show, they advanced cautiously and came to their conclusions only after long and painstaking experimental studies. The literature will be reviewed in sufficient detail to bring out some of these points.

The present popularity of chest leads as a routine electrocardiographic procedure, coming almost immediately in the wake of the introduction of Lead IV, and the type of literature and investigations which the introduction of this special lead has prompted warrant at this time a critical review of the literature as well as a careful examination of the rôle of chest leads in general, and of Lead IV in particular, as aids in clinical electrocardiography. Such an examination at this time may lead to a clearer understanding of the investigations which the introduction of Lead IV has prompted in the past and may point out the directions in which it further tends to stimulate the study of electrocardiography.

In reviewing the early literature, one gains the unavoidable impression that, in the enthusiasm attending the introduction of Lead IV, articles dealing with the subject have, perhaps inadvertently, underrated abnormal findings in the standard leads in cases used to illustrate the diagnostic advantages of chest lead tracings and that they have correspondingly overemphasized the relative diagnostic value of abnormal chest lead findings. Such overemphasis has been exemplified in the literature by the use of terms, such as "specific" and "pathognomonic," in describing tracings derived by Lead IV, while obviously abnormal standard lead tracings are often characterized as having "no diagnostic value." These statements will be strengthened by direct references to, and quotations from, leading early articles on the subject.

Although some of the comments accompanying the review of the literature may seem unduly critical, it should be understood at the outset that there is no intention to underestimate the value of contributions presented by pioneers in this field. It is recognized that the work of some, Wolferth and Wood in particular, has been in a measure inspiring and unquestionably stimulating. It is precisely because of this, that a critical review seems timely. It is hoped that such a review at this time may tend to prevent publications based on limited experience and meager information from creating impressions about the value of chest leads

which the originators of this work probably never intended to create. There is also this to be considered. Minor changes in the ventricular complexes of the standard leads, though imperfectly understood today, may prove to have a very significant meaning; but, if as a result of our enthusiastic preoccupation with chest leads we cultivate the tendency to underrate minor changes in standard leads, electrocardiography may suffer a setback. And it may be stated safely that no particular chest lead or leads will displace the standard electrocardiogram, perhaps not even in the study of localized myocardial damage. Standard electrocardiography is built on a firm foundation. It is the creation of a master mind. Its three components are not only distinctive and individually informative, but they have the additional advantage of being interrelated with an almost mathematical precision, leading to wide information on cardiodynamics, beyond the province of chest leads. Furthermore, as pointed out by Wilson, the standard curves are comparatively unaltered by shifting of the electrodes. They remain constant and reliable in form. This is not true of chest leads.*

This brief digression into the properties of the standard electrocardiogram and the implied caution that minor changes be not considered as having "no diagnostic value" will appear more significant as we enter upon the review of the literature.

In their original article Wolferth and Wood[1] report two cases with clinical evidences of coronary occlusion. They state that Lead IV showed "unmistakable deviation" while the standard leads "yielded little or no diagnostic information," except on the fourth day. Actually, perusal of their graphs reveals that the standard leads were also definitely abnormal. The first case, to be sure, showed only a shallow T_1, which in the course of four days took on the form of a high take-off. However, in their second case the standard leads showed not only a shallow T_1 but also a definitely elevated RS-T segment. Furthermore, the standard electrocardiograms in both cases showed progressive changes from day to day. This we know to be strong presumptive evidence of myocardial damage. The authors stress this important point also.

In their next publication,[2] these investigators promptly caution against laying undue emphasis on the importance of Lead IV. They conclude that "the purpose of the paper is to show that Lead IV does not in any way replace the routine electrocardiogram but should be used as an adjunct to it."

Some of the other writers, however, had apparently failed to heed this timely warning. At any rate, they seemingly did not examine their standard leads critically and had almost uniformly conveyed the impression that it is the chest lead which serves as the ultimate criterion in

*Wilson[3] pointed out that shifting the limb electrodes over different parts of the extremities, with the galvanometer string at normal sensitivity, does not appreciably alter the standard electrocardiogram, provided the electrodes remained on the limb. However, if one electrode is transferred to the trunk, definite changes are noted. These become more and more pronounced as the electrode approaches the region of the heart.

the diagnosis of myocardial involvement. The several case reports which followed in the wake of these two publications clearly show an overemphasis of the diagnostic value of chest leads, while they generally refer to the standard leads accompanying them as showing "inconclusive changes."

One of these reports[3] refers to two cases of coronary occlusion. The first case is that of a man forty-four years old with previous hypertensive heart disease and a history of *status anginosus* four days before admission. Three electrocardiograms were taken, one week apart. In this case the standard leads show definite changes indicative of myocardial damage while the chest lead shows only a corresponding T-wave abnormality. Yet, the authors make the startling statement that the "tracings show a pathognomonic R-T anomaly in the chest lead at the time that the conventional leads show only inconclusive changes." Actually the chest lead shows only a diphasic T_4 and a very slight depression of $(R\text{-}T)_4$, approximately 2 mm. As their second case, these authors present an electrocardiogram consisting of four leads taken about six months after a coronary episode. Lead IV shows an upright T-wave. The authors present this case as an evidence of the persistence of a "chest lead anomaly six months after a coronary occlusion." No mention is made of the fact that T_1 of the standard leads in this case also shows a conspicuous inversion (patient had no hypertension). The upright T_4 is obviously the usual counterpart of an inverted T_1. This article clearly overemphasizes the diagnostic importance of the chest lead while it definitely underrates the value of the standard leads.

Another report[4] refers to three cases. The first of these cases is irrelevant. The patient had three successive seizures of angina pectoris. He died during the last attack. Standard leads were taken after the first seizure. They were not significant. No chest leads were taken. The case is recorded in a tone of implied regret, expressing the assumption that if Lead IV had been taken, myocardial damage might have been disclosed. The second case is presented merely as an example of an abnormal Lead IV. In this case the standard leads are also definitely abnormal and are suggestive of a left coronary occlusion (T_1 type). The third case is important in that a diagnosis of coronary occlusion is made on Lead IV alone. This is a case of a thirty-nine-year-old man who had given a history of an occasional substernal pain "on bending over or picking up heavy objects." One day, while at rest, he became dizzy and developed continuous precordial pain, lasting fifteen hours. The pain was not intense; it was "bearable." He received morphine to relieve his "nagging" pain. Physical findings were negative. Electrocardiographic standard leads were normal. With reference to the chest lead the writer states that "Lead IV was characterized by a depressed S-T interval and an inverted T-wave." The case report concludes: "This, with the clinical history justified the diagnosis of a coronary occlusion,

in spite of the meager physical findings." The depression of $(S\text{-}T)_4$ referred to was less than 2 mm., and the negative T-wave in the chest lead was obviously not abnormal. (Case 3, Fig. 4, pp. 422, 423 of publication cited in reference 4.) This case report is discussed at length because it is an example of overestimating the meaning of Lead IV. The clinical diagnosis in this case may have been correct, but the chest lead certainly was not the determining factor in the diagnosis as the conclusion implies. This is clearly an example of overemphasis, definitely not in accordance with the intentions of the original investigators who introduced Lead IV, as subsequent reference to their work will show.

Liberson and Liberson[5] report a series of 75 cases of which 20 were normal, 50 "cardiac suspects," and 5 "coronaries." They have modified the technic of Wolferth and Wood in that they placed the L electrode anteriorly and the R electrode posteriorly, presumably with the purpose of having the main deflection of the chest lead follow the direction of similar deflections in the standard leads. They established criteria for the normal chest lead which were essentially the same as those of Wolferth and Wood, except that in their modified chest lead the main deflections have opposite directions. In their "Lead IV," naturally, the initial ventricular complex has a conspicuous S-wave instead of the Q-wave, and the T-wave is upright. (Wolferth and Wood in their original paper stated that this arrangement of the electrodes was optional.)

These writers report an illustrative case to show that the chest lead may point to a diagnosis of coronary occlusion, "where neither the clinical picture nor the standard leads suggest it." It is true that the chest lead in this case showed a conspicuous deviation of the RS-T segment, suggestive of an acute myocardial involvement; yet, the clinical picture and standard leads taken at this time were also highly suggestive. The patient complained of an "upset stomach" and had a fall in blood pressure from 170/90 to 120/66. Furthermore, the standard leads showed diphasic T-waves in Leads I and II with definite "coving" of their first portion.

The authors state, furthermore, that in this case the S-T changes noted in the chest lead occurred "fully three weeks *before* similar changes in the standard leads" [italics mine]. This is apparently an erroneous conclusion, based on an imperfect appraisal of the clinical history. According to their records, the patient in question left the hospital after his first attack, "improved." He was readmitted fourteen days after the first tracing had been taken, because of an attack of abdominal and chest pain associated with dyspnea. On readmission, he was "acutely ill" and had a thready pulse, temperature, and leucocytosis. Electrocardiograms taken five days later showed marked S-T changes, but this time the changes appeared in Leads II and III of his standard electrocardiogram. The chest lead showed only a shallow T-wave, and no S-T deviation. This patient apparently had a fresh myocardial insult (a pos-

terior wall injury) revealed this time by the standard leads only and the changes in the standard leads were *not*, as the authors indicate, "the appearance of changes at a later date—three weeks later."

In a study of Lead IV, Katz and Kissin[6] examined a group of normal individuals and some with myocardial disease, including eleven who had recent coronary closure. On comparing Lead IV with standard leads in the same patients, they grouped their cases as follows: (1) those with characteristic changes in Lead IV and the standard leads; (2) those with characteristic changes in the standard leads only; and (3) those with characteristic changes in Lead IV only. Their standard lead tracings in subgroup (3) though not "characteristic," are nevertheless abnormal (Fig. 3e, 4a, 4b, 4c in the article cited in reference 6). At any rate, in a strict sense, the group does not show changes in "Lead IV only."

They add their eleven cases to the five previously reported by Wolferth and Wood and state that seven out of this group of sixteen cases "show specific changes in Lead IV only." The changes in the standard leads accompanying Lead IV in this group are not conspicuous, to be sure; yet these tracings show definite abnormalities, sufficient to indicate myocardial involvement. At any rate, the changes in this group are not confined to Lead IV only. Furthermore, the designation of the cardiographic changes in Lead IV as being "specific" is open to objection. The validity of such a designation would depend essentially on the interpretation of the tracing in the light of a clinical syndrome. As a diagnostic criterion in structural heart disease no electrocardiogram per se may be termed specific. The instrument essentially records physiological events. It depicts anatomical changes by inference only. As further evidence that the term "specific" is not a suitable designation for abnormalities in tracings derived by Lead IV or, for that matter by any lead, these writers themselves add in their summary that "the presence of any abnormalities in Lead IV are to be considered in the same way as abnormalities in the ordinary lead. . . . They are less significant when they occur alone than when they are accompanied by other electrocardiographic evidence pointing in the same direction." In the light of these statements then, may it not be asked, "Wherein are they specific?"

Hoffman and Delong[7] reported a study of chest leads of 125 normal cases and a small series of pathological cases. These writers emphasize an important point worthy of special note, namely, that there are changes in the chest lead tracings on slight change in the position of the anterior electrode.

Their pathological cases they group as follows: (1) those showing normal standard leads and abnormal chest leads; (2) those showing abnormal standard leads and abnormal chest leads; and (3) those showing abnormal standard leads and normal chest leads.

In their first group designated as showing normal standard and abnormal chest leads, careful examination of the tracings clearly reveals minor variations in the standard leads (shallow T_1 and T_2, slight inversion of T_1, low voltage QRS, and shallow diphasic T_1 T_2). These changes are sufficient to stamp these standard leads abnormal. In fact, they are suggestive of anterior lesions in those patients who have had a coronary episode. In their third group in which the standards were abnormal and the chest normal, the standard leads show conspicuous changes of the T_2 and T_3 type. This group exemplifies the limitation of chest leads and the indispensability of standard leads.

These workers confirm the important observation of Wolferth and Wood, that at times changes in the chest lead do appear before they are conspicuous in the standard leads. This is a valuable property of chest leads when present. But these workers add, what seems equally important, that frequently chest leads revert to normal before the standard leads. The importance of this lies in the fact that it lends emphasis to the interdependence of chest leads and standard leads. Where one fails, the other may aid. They observed also that in a few instances the chest lead remained abnormal for many months after the standards became normal. This is interesting, but the question may be raised as to what criteria have been used in the evaluation of the standard leads. From the literature reviewed thus far it appears that, while we are busily preoccupied with establishing criteria for chest leads, we seemingly have not as yet agreed on uniform criteria as to what constitutes a normal standard electrocardiogram. When standard lead tracings are properly evaluated, it is found that they, too, remain abnormal for many months, at times even for years.

Goldbloom[8] reports 25 normal cases and a group of 40 ambulatory cardiac cases. Out of the latter group, 13 were previously observed and treated for coronary artery disease with thrombosis. In his studies the writer had used anteroposterior as well as posteroanterior chest leads. He concludes that 30 per cent of his cases of coronary thrombosis show an abnormal Lead IV, "whereas the routine three leads are negative." This conclusion is based on 13 cases of which 4 cases constitute the 30 per cent. The writer presents a table of relative "evaluation" of the four leads in this group (p. 496 of publication cited in reference 8); but the table actually fails to show normal standard leads in the four cases mentioned as constituting the 30 per cent. Two of these cases show abnormal T-waves in two out of the three standard leads. The third case shows a negative T_2 (the T-wave must therefore be negative in one other lead). The fourth case has a diphasic T_3 (here, Lead I must also be diphasic, if the galvanometer string is of the same standard tension in both leads). In a measure, the writer is justified in his conclusion, if regarded in the light of the criteria he sets for his standard leads. For an abnormal standard electrocardiogram to be indicative of

myocardial damage, he requires a "high take-off of the T-wave" or "diphasic T-waves in more than one lead." On the other hand in setting criteria for an abnormal Lead IV, he makes no corresponding requirement, such as a deviation of the RS-T segment. He regards Lead IV abnormal whenever the T-wave is "absent" or "upright" but does not stress an equally significant shallow or inverted T-wave in Lead I. In conformity with previous articles, here too, the writer presents a case to illustrate that an abnormal Lead IV may persist for a long time after a coronary occlusion. He does not mention, however, that the accompanying standard leads *also* show *a definitely* abnormal T-wave in Lead I, which is equally important.

These articles and case reports, dealing with chest leads, are interesting and instructive in that they disclose a strong tendency to overemphasize the value of a diagnostic procedure which as yet has been but imperfectly mastered. This tendency bespeaks a wish, it seems, for an open sesame into the hidden realms and manifold sequestered channels that lead to a diagnosis in cases of myocardial disease. Practically all tracings presented as groups showing normal standard leads with abnormal chest leads, actually show abnormal standard leads as well. These abnormalities, to be sure, are not conspicuous. They are characterized by a shallow or inverted T-wave *only*; but the abnormalities in the standard tracings of the group are generally confined to Lead I or Leads I and II. Such findings are clearly abnormal and are often indicative of myocardial damage. This was recognized very early in electrocardiography. Even Einthoven[7] in his early studies on the electrocardiogram clearly pointed out not only that T_1 and T_2 are normally always upright but that "if one finds a shallow or negative T-wave in Lead I or in Leads I and II, one deals with a diseased heart muscle, whose pathological deviation denotes a muscular insufficiency or *myodegeneratio cordis.*"

Furthermore, in cases cited in the literature as showing "conspicuous," "specific," or "pathognomonic" changes in Lead IV, while the accompanying standard leads presumably showed no abnormality, we find that such changes in Lead IV were indicated in the majority of cases only by an abnormally directed T_4. This, however, may not be taken as a pathognomonic change. It does not necessarily denote any more than an abnormally directed T_4.

A perusal of the records and a study of the data published in the literature, added to personal observations, point convincingly to the fact that a considerable number of electrocardiograms showing abnormal standard leads *are not* accompanied by abnormalities in Lead IV, and, furthermore, that an abnormal Lead IV with a normal standard electrocardiogram is extremely rare. The point seems to have been missed uniformly, that a conspicuous, abnormally directed T_4 cannot be present in an electrocardiogram which has a well-defined, normal, upright T_1. The two are incompatible.

The confusion that attended the early literature on chest leads (Lead IV) has been considerably clarified by the appearance of an article by Wood and Wolferth[10] on experimental coronary occlusion. This communication deals with carefully controlled experiments in which these workers occluded major branches of the coronary arteries through slits in the pericardium. With this technic, the anterior surface of the heart not being exposed, they were able to record electrocardiographic changes in chest leads of anterior as well as posterior lesions. The changes in the chest lead tracing, which they emphasize, is the RS-T deviation and not the much-misunderstood T-wave. The abnormal T-wave is a later change. The chest lead tracings in these modified experiments, they observed, resembled very closely those derived by leads taken directly from the hearts of their experimental animals. It was this observation which led to the use of the anteroposterior chest lead in human subjects suspected of coronary occlusion. Unfortunately, this publication appeared late. It was held up "in press" for about thirteen months. The cardinal points brought out by these experiments may be summarized as follows:

1. Occlusion of a major branch of a coronary artery produces an RS-T deviation within about two minutes.

2. With the R electrode placed anteriorly and the L electrode posteriorly, an *anterior infarct* produces a *depression* of the RS-T segment while a *posterior infarct* produces an *elevation*.

3. The results are similar to those obtained by leading directly from the heart.

These workers do not claim that their findings in the dog are necessarily transferable to man. In this article, as a further aid in diagnosis, they advise *also* additional chest leads, namely, from apex to foot and from dorsum to foot, Leads V and VI.

The subject of chest leads in the study of coronary occlusion takes on new and added interest as we follow the work of Wood and Wolferth and their collaborators. In one of their more recent publications[11] they present electrocardiographic observations and report necropsy findings in cases that were studied by means of three standard leads and three chest leads. They confirm their previous conclusion to the effect that in an acute anterior infarction, in addition to whatever the standard leads may show, chest leads, especially Leads IV and V, show a conspicuous negative deviation of the RS-T segment. They report, furthermore, that in this type of myocardial damage the initial negative component of the QRS, seen in the normal chest lead, tends to disappear. This has been pointed out also by Wilson, Barker, Macleod, and Klostermyer.[12] As recovery takes place, Wood and Wolferth maintain that the negative RS-T deviation gradually gives way to an upwardly directed T-wave; but that the initial negative component of the QRS which disappeared during the acute injury does not tend to reappear for some time.

To this observation the writers attach considerable importance. They believe that an absence of the characteristic initial downstroke of the ventricular complex in chest lead tracings denotes a residual stigma. In other words, that the absence of a Q-wave in Leads IV and V may be taken as presumptive evidence of a prior injury to the anterior ventricular wall along the course of the anterior descending branch of the left coronary artery. This is an interesting observation indeed and, if confirmed in a sufficiently large series of cases, will serve to establish the value of chest leads more securely as a routine procedure in clinical electrocardiography.

In this article the writers reiterate their previous statement to the effect that in coronary artery occlusions which produce infarctions of the posterior ventricular wall, chest leads "often show no abnormal findings." In such lesions it is well known that changes in the standard Leads II and III stand out preeminently and by far overshadow the chest leads. Yet, since in these lesions standard Leads II and III as well as chest Leads IV and V generally show also conspicuous negative deflections of the first limbs of the QRS complexes, namely conspicuous Q-waves, the chest lead tracings may serve an important purpose in possibly disclosing a previous anterior wall injury. This they might disclose by the absence of Q-waves, the residual stigma discussed in the foregoing paragraph.

In the light of the foregoing, chest leads may then be viewed as being of aid at least in two perplexing clinical problems relating to injuries of the left ventricular myocardium. A conspicuous deviation of the RS-T segment may be regarded as being indicative of an acute or recent injury, and the "residual stigma"—absent Q-wave—of an old injury to the wall of the left ventricle.

Thus the literature on chest leads, although in the main insufficiently informative, leads us nevertheless to the conclusion—essentially on the basis of the work of Wolferth and Wood—that evidences of certain types of myocardial damage may be disclosed by special leads in which one electrode is located over the precordium. This does not imply that the methods employed at present necessarily serve fully to carry out this purpose. In fact, there remains a seeming need for a proper appraisal of the methods now in use, particularly since chest leads, judged by the popularity they have attained, probably are destined to remain as an integral part of clinical electrocardiography.

In order to maintain a proper perspective in our endeavor to evaluate special leads as aids in clinical electrocardiography, let it be recalled that electrocardiography by means of chest leads is not new. In fact, it is one of the oldest of cardiographic procedures. The first human electrocardiogram ever reported was derived by means of a chest lead. Waller,[13] using the capillary electrometer in the study of the electrical effects of the human heart and desiring tracings with maximal deflections,

employed apex leads. Einthoven and deLint,[14] in a study of the relative forms and amplitudes of the principal components of the electrocardiogram in human subjects under alternating conditions of rest and vigorous exercise, found it convenient to use chest leads. It was their object to record the greatest possible deflections in order that they might evaluate minor differences in the amplitudes of corresponding complexes, as a result of removal of vagus tone by exercise.

Shortly after the introduction of the string galvanometer, however, chest leads were discarded as a routine procedure in the study of the electrical effects of the human heart. The string galvanometer yielded ample deflections in limb leads. Furthermore, the limb leads finally chosen by Einthoven had proved to have certain remarkable properties not possessed by chest leads. They were found to be related to one another and to a common hypothetical resultant electrical axis, so that all three could be expressed as functions of a single variable. This interrelation permitted interesting calculations as to the value of the manifest body potential as well as to the behavior of the electrical axis in hearts of certain size and configuration.[15] In addition, the constancy in form and amplitude of any one of the three limb leads in relation to synchronous events in either of the other two leads stood out in great contrast to the inconstancy of tracings derived by means of chest leads. Soon after the introduction of the string galvanometer, therefore, particularly as a result of the recognition of the properties of limb leads, it was a natural consequence that chest leads as a routine should be discarded. After this, chest leads may be said to have been employed only in special investigations, especially in those concerned with the study of individual components of the electrocardiogram in certain types of abnormal heart action, or in the study of special physiological problems dealing with the spread of the excitation wave and the distribution of the cardiac potential. Some of these special investigations by means of chest leads are particularly noteworthy in that they have dealt with fundamental problems in electrocardiography.

Lewis,[16] in demonstrating that the oscillations in the electrical curves of auricular fibrillation emanate from the auricles, employed combinations of precordial electrodes. He had shown that these oscillations became more and more conspicuous as the exploring precordial electrode approached the vicinity of the right auricle.

Wilson,[17] in a study of the potential differences produced by the heartbeat within the body and at its surface, employed precordial electrodes. It was in this study that he made the interesting observation that in the case of chest leads "it is the electrode near the heart which determines the form of the ventricular electrocardiogram." He showed also that "it matters little where the second electrode is placed, providing it is sufficiently far away from the heart."

In a study of the relation between the anatomical and electrical axis of normal as well as hypertrophied hearts, Cohn and Raisbeck[18] used symmetrically arranged chest electrodes, the locations of which on the anterior chest wall corresponded to the apices of a rotating equilateral triangle.

With the aid of precordial electrodes, Wilson and his coworkers have made several valuable observations on the nature of bundle-branch block. By means of serial precordial leads from several points across the lower anterior chest, from right to left, they were able to show the order of excitation of the ventricles in human bundle-branch block.[19] More recently[20, 21] with a similar system of exploring chest electrodes but with the additional aid of an ingenious device affording a second, strictly neutral electrode, they have been able to decipher certain types of abnormal human electrocardiograms as belonging to the category of right bundle-branch conduction defects. This method of study (unipolar electrocardiography) has tremendous and far-reaching possibilities. It may prove to be the key to an entirely new approach in the study of electrocardiography.

A report of Wilson, Barker, Macleod, and Klostermyer[12] is of particular interest in connection with the subject of this paper. This communication may be deemed a connecting link between the many and diverse electrocardiographic studies by means of special leads in the past and the more recent work of Wolferth and Wood which has since led to the present popularity of chest leads as a routine cardiographic procedure. This report is primarily concerned with anomalies in the initial ventricular complex (QRS) in coronary occlusion as deciphered by the standard leads. In this report the writers, however, recorded tracings by means of chest leads as well, and they point out also characteristic changes in the initial as well as the terminal ventricular complexes of chest lead tracings in cases of anterior and posterior cardiac infarction as a result of coronary thrombosis.

The subject of chest leads naturally leads one to the experimental, pathological, and clinical observations of Wolferth and Wood,[1, 2, 10, 11] which in the aggregate mark an important milestone in electrocardiography. Their observation of an early, conspicuous RS-T deviation in direct leads employed in experimental coronary occlusion and, particularly, their further observation that such deviations in the terminal ventricular complex when recorded by means of an anteroposterior chest lead are essentially the same as those derived by direct leads, has naturally suggested the use of chest leads in human subjects suspected of coronary occlusion. Throughout their publications they lead toward one seemingly cardinal point: namely, that in certain cases of acute coronary occlusion, especially those producing infarction in the course of the anterior descending branch of the left coronary artery, the chest lead may show the earliest evidence of an acute myocardial damage. Such a

lesion is indicated by a deviation of the RS-T segment, which, as recovery takes place, is followed by an abnormal direction of the T-wave. In the case of their special chest lead, designated as Lead IV, the abnormal T-wave is positive—directed upward. This chest lead of Wolferth and Wood, together with Leads V and VI which they subsequently suggested, constitutes the conventional set of chest leads now generally employed in clinical electrocardiography. As such they merit special comment. This is particularly true of Lead IV.

Lead IV, then, is a special lead in which two electrodes are placed in contact with the chest wall; one, the right arm electrode, in the vicinity of the cardiac apex, and the other, the left arm electrode, in the left paravertebral space above the level of the angle of the scapula. The tracing derived by this lead is well known. Its features have been care-

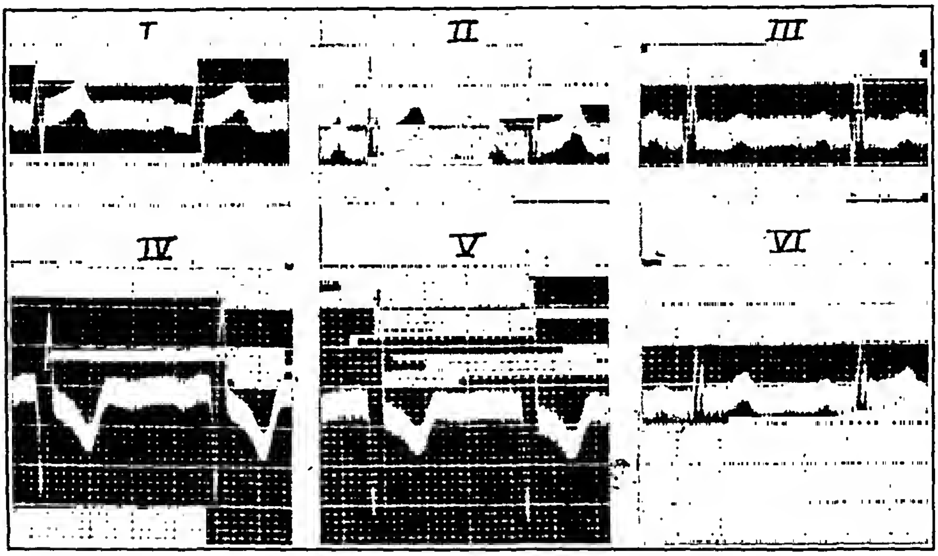


Fig. 1.—Standard Leads I, II, and III compared with the conventional chest Leads IV, V, and VI. For description see pages 811 and 812.

fully described at the time of its introduction and have been subsequently verified by others in studies aggregating hundreds of normal subjects.[5, 6, 7, 8, 22] The tracing is characterized by: (a) an inverted auricular (P) wave, (b) a diphasic initial ventricular complex (QRS), and (c) an inverted terminal ventricular (T) wave.

Besides these characteristics, the individual components of this electrocardiogram have other peculiarities. The auricular P-wave is very shallow; the initial ventricular complex is large and begins with a downstroke—a Q-wave; the T-wave is large. The RS-T segment has practically no isoelectric period (Fig. 1). Occasionally there is normally present in Lead IV a slight negative deviation of the RS-T segment, of one or two millimeters. This is probably an artefact due to overshooting of the galvanometer string.

These criteria are best remembered if we regard Lead IV as a magnified, partly inverted Lead I rotated through an angle of 90°, bringing the lead axis into a plane parallel to the sagittal instead of the coronal plane of the body. The magnification is confined to the ventricular complex and is due to the fact that one electrode is situated in a region where the heart is nearest to the chest wall. The inversion of the principal components of this tracing, as compared with those of standard Lead I, is due to the right arm electrode being situated in the vicinity of the cardiac apex. (In standard leads this electrode is nearer to the basal region of the heart.) Rotation is suggested by the shallow negative P-wave and the diphasic QRS.

As has been stated, Wolferth and Wood advocate a set of three chest leads. In addition to Lead IV they employ also Leads V and VI. The tracing of a normal Lead V is essentially of the same general configuration as that of Lead IV, in spite of the fact that the electrode which in Lead IV is located near the left scapula is attached in this lead to the left foot. The reasons for the similarity between these two tracings will be discussed in another paragraph. Lead VI, on the other hand, bears practically no resemblance to either of the other two. This is a lead from the left scapula to the left foot. It yields a rather indistinct and a considerably stunted tracing. It generally resembles a miniature Lead III (see again Fig. 1).

The carefully described criteria for Lead IV (or for any chest lead) are but gross at best. There are many factors to prevent a constancy in the form of chest lead tracings. Among these are: dislocation of the anatomical axis of the heart in extremes of habitus, as in short wide chests or long narrow chests; the amount and the kind of media interposed between the cardiac apex and the electrode, as in obesity, emphysema, or intrathoracic effusions; inaccuracy in locating the apex impulse; or shifting of the "apical" electrode. The last mentioned factor is of importance. Hoffman and Delong[7] in their study of normal lead IV found appreciable alterations in their tracings on slight changes in the position of the anterior electrode. Wood, Bellet, McMillan, and Wolferth[11] also stress this. They caution, in fact, that when "small electrodes are used, a relatively small change in the position of the anterior electrode may cause considerable alteration in the tracings." The effect of changing the position of the anterior electrode on the form of the ventricular electrocardiogram is illustrated in Fig. 2.

Since it exerts a definite controlling effect on the form of the resulting curve, the anterior electrode in chest leads may be designated as the principal electrode. The posterior electrode, on the other hand, may be termed an indifferent or at best a secondary electrode. That the position of this electrode is comparatively immaterial has been pointed out by Wilson[17]—to quote: ". . . the position of the second electrode so long as it is relatively distant from the heart has little effect on the ventricular

electrocardiogram." This is verified and illustrated in Fig. 3. Serial electrocardiograms were taken with a fixed anterior electrode and a shifting posterior electrode, placed successively on the right arm, right scapula, left scapula, left lumbar region, and left foot. They show no appreciable alteration in the form of the ventricular curve, except for

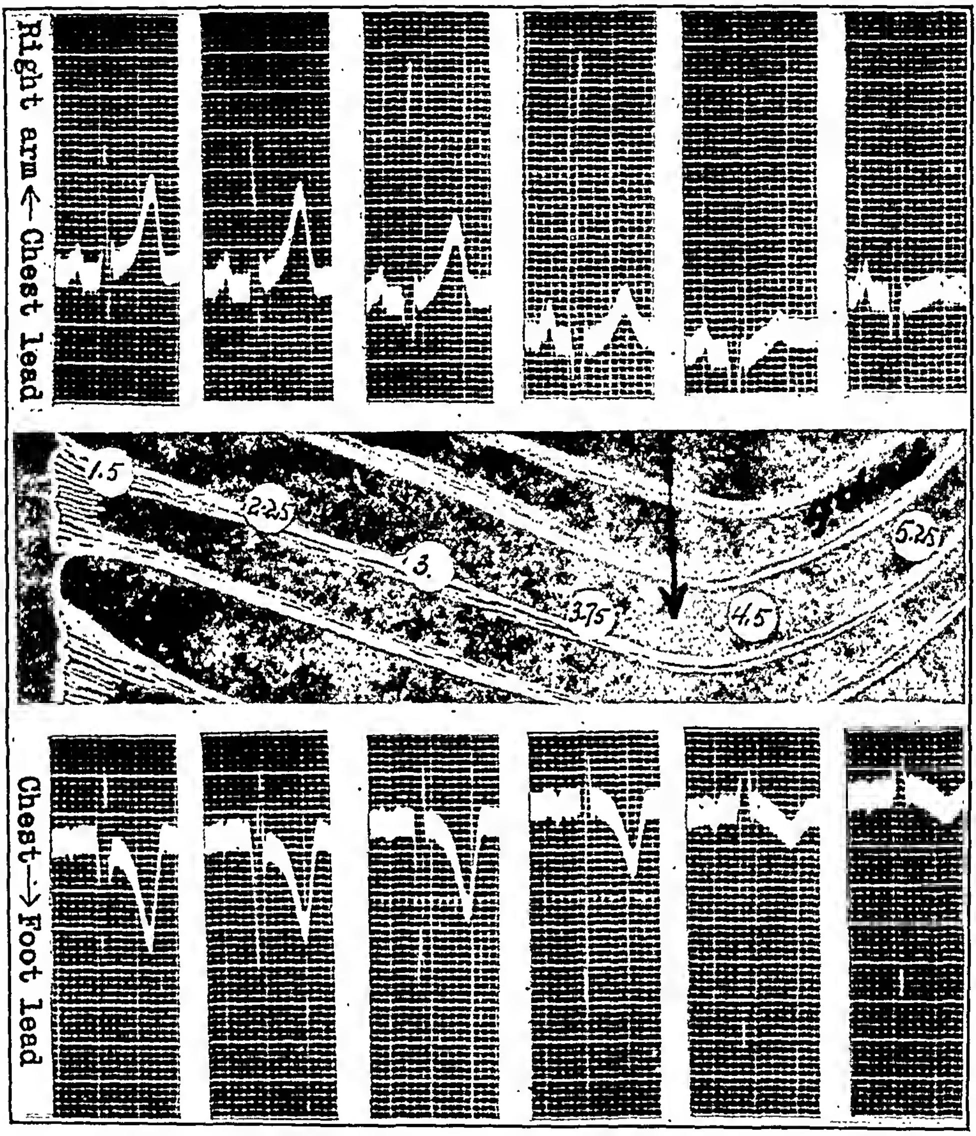


Fig. 2.—The effect of shifting the principal electrode on the form of the ventricular electrocardiogram.

As indicated in the diagram accompanying the graphs, the principal electrode was applied over successive zones approximately 0.75 of an inch apart, along a line beginning at a point 1.5 inches from the midsternal line and extending to the left for a distance of about 3.75 inches, or 5.25 inches from the midsternal line. The region of the apex impulse is indicated by an arrow.

In both the upper and lower rows the first four graphs, recorded from zones between the left sternal margin and cardiac apex, show T-waves of fairly constant form. The last two graphs, recorded from zones between the apex impulse and a point 1.25 inches beyond, show a sharp fall in the amplitude of the T-waves and a corresponding rise in the QRS complexes. The upper row of graphs were recorded by leads from right arm to chest, and the lower row, by leads from chest to foot. The chest electrode was attached to the left arm cable. Its diameter was approximately 1 inch. The chest foot lead is identical with Lead V of Wolferth and Wood.

slight changes in amplitude.* Even if tracings were not presented to demonstrate this, ample evidence may be had by comparing Leads IV and V of Wolferth and Wood. Lead IV, as has been stated, is derived by means of an apical electrode and a second electrode in the region of the left scapula, while Lead V is derived by means of the same apical electrode but with the second electrode attached to the left leg or foot. Yet, the forms of these two tracings are similar in many details, giving evidence of the "indifference" of the second electrode. So obvious is the similarity between these two tracings, although derived by two distinctly different leads, that some laboratories have adopted the use of Lead V instead of Lead IV as a matter of bedside convenience in clinical routine.

The manner of application of the chest electrodes (R electrode anteriorly and L electrode posteriorly), as originally adopted by Wolferth and Wood, is open to some objections. To those with limited experience, Leads IV and V may appear at first glance as somewhat distorted, magnified, mirror pictures of Lead I of the standard electrocardiogram. And there is some reason for this impression. Lead IV does "mirror" primarily the standard Lead I. Abnormalities in Lead IV, when accompanied by abnormalities in the standard leads, are generally paralleled by Lead I only. Both, Lead IV and Lead I generally depict the same lesions of the ventricular myocardium, namely, anterior surface lesions. Yet, when these two tracings are viewed side by side, one is struck by the marked dissimilarity between their synchronous components. Synchronous deflections in the two leads have diametrically opposite directions. This at first glance tends to some measure of confusion. The chest lead tracing has a strange configuration. In fact, it requires the study of a new set of criteria in which the principal components of the electrical curve are expressed in negative values.

Yet, there is some justification for the manner of application of electrodes as advocated by Wolferth and Wood. If the apical electrode is to represent the exploring electrode used in experimental direct leads and if it is desired that the potential variations beneath this electrode be recorded in positive values, the R electrode must be applied anteriorly. In fact this is precisely why an "inverted" Lead IV came into clinical use. As has been stated, Wolferth and Wood, employing direct leads in experimental work, used the R electrode as the exploring electrode. It was with this technic that they first recorded characteristic RS-T deviations in experimental coronary occlusion, showing a *depression* of the RS-T segment in *anterior lesions* and an *elevation* in *posterior* lesions. By a cleverly contrived experimental procedure, they showed furthermore that if the anterior surface of the heart was not exposed, they could duplicate these electrocardiographic changes by means of chest leads. To demonstrate the striking similarity between curves derived by direct

*This is not true for the auricular P-waves. See again Fig. 3.

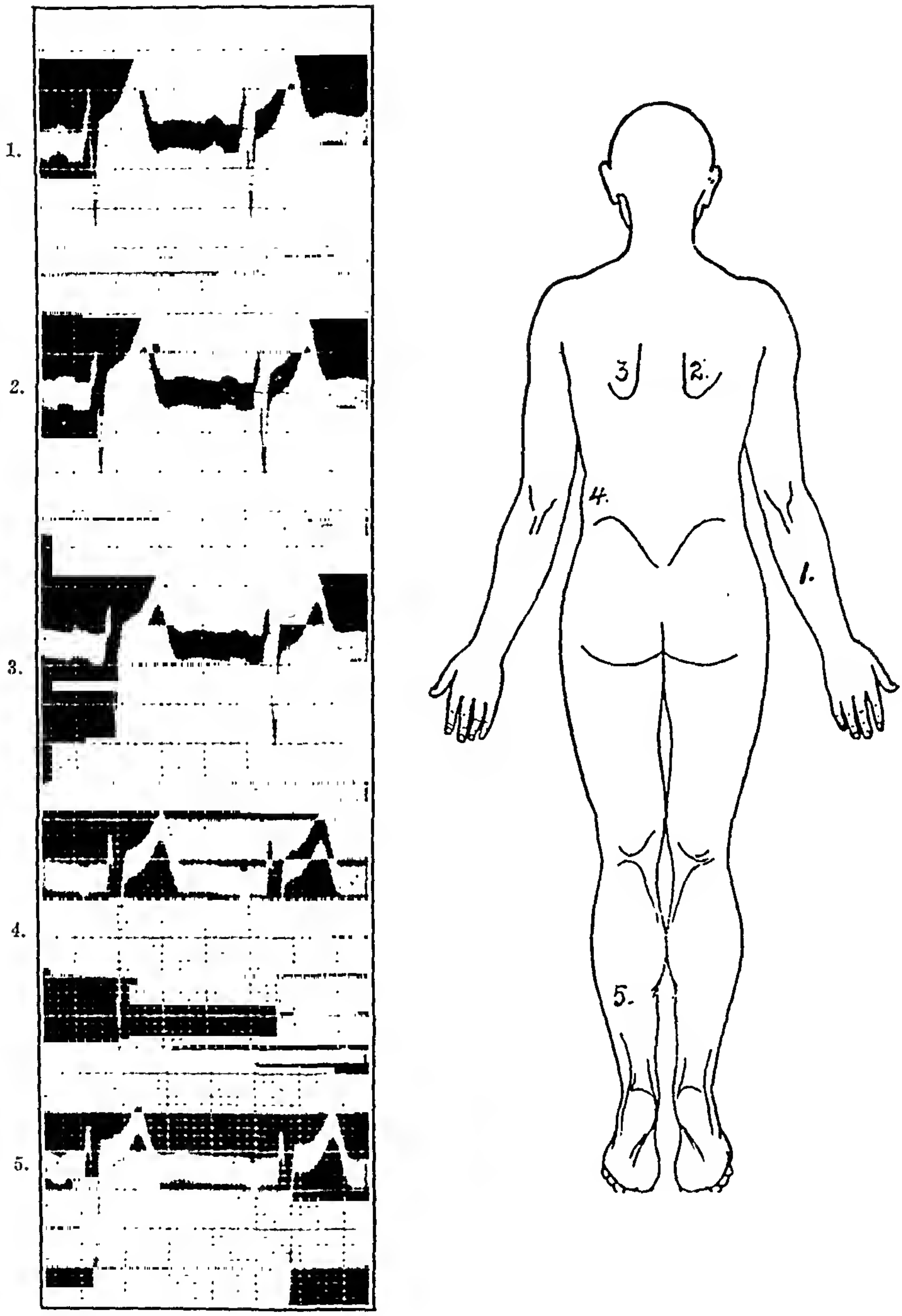


Fig. 3.—The effect of shifting the second or "indifferent" electrode on the form of the ventricular electrocardiogram.

As indicated by the numerical notations in the diagram accompanying the graphs, the right arm electrode was applied successively over widely separated regions on the surface of the body. The graphs show that the ventricular curve is practically unaffected except for slight changes in amplitude. On the other hand, the auricular P-waves are definitely altered.

In all these "leads" the principal electrode was held in exactly the same fixed position, in the region of the apex impulse. See footnote on page 826.

leads and those derived by chest leads, they naturally had to employ the same relative method of application of electrodes, that is, the R electrode as the anterior electrode. This had automatically set criteria for their chest lead analogous to those of their direct lead; and these criteria, expressed in negative ordinates, were eventually transferred, with the clinical adoption of chest leads, to the study of coronary occlusion in man.

Nevertheless, this manner of grouping of chest electrodes when carried over to clinical investigations has, it seems, certain disadvantages. Ever since its introduction, Lead IV has been advocated as an *aid* to the standard leads. It was never to replace but merely to complement the standard leads. The standard electrocardiogram and the chest lead tracing were intended to appear as a group. Such being the case it would seem desirable that some measure of symmetry characterize this group. To this effect a chest lead, taken with the L electrode applied anteriorly instead of the R electrode, would afford such a symmetry in that all deflections in the chest lead would then correspond in direction to those of the standard leads, for all identical events in the cardiac cycle. Lead IV as recorded at present fails to afford this much desired symmetry. In fact, in its present form it has necessitated the learning of a set of new criteria depicted in negative ordinates.

Furthermore, the scapular application of the posterior electrode as employed in the conventional Lead IV seems unnecessary. At times it may even prove somewhat burdensome. In the case of an acute coronary occlusion in which the chest lead is presumed to subserve the greatest usefulness, the patient may be and frequently is acutely ill; at times he is moribund. The application of a posterior electrode under such circumstances may offer a difficulty to the operator and an annoyance to the patient. In such a case simplicity of technic is most desirable. This is probably the reason why some clinicians have adopted the use of Lead V alone and have discarded the original Lead IV.

The numerical designation of chest leads introduced by Wolferth and Wood is also open to objections. The designation "Lead IV" implies a relationship to the standard Leads I, II, and III. Actually, while the standard Leads I, II, and III are strictly related to one another (components of a common vector), Lead IV bears no such relationship to any one of them whatever. As a matter of fact, Lead IV is not even a fixed lead. The principal electrode which actually determines its form is at times applied by some workers to the left parasternal line in the fourth space, and at other times to the region of the cardiac apex. The numerical designation of Lead IV does not specify the point of application of the principal electrode, which, as has been shown, actually determines the form of the resulting electrocardiogram. The only thing about this lead that may be regarded as relatively fixed is the posterior electrode; and this, as has been stated, is practically immaterial. In the case of

standard leads the numerical designation of a lead implies a specific location of the electrodes,* and the numerical designation employed carries the same connotation wherever electrocardiography is done. This, not being true for chest leads, suggests the necessity of more specific designations. This statement takes on added weight if we take into consideration the fact that the present popularity of chest leads has prompted many investigators to "tap" the chest in innumerable directions for special chest leads. To designate all such leads by numbers will ultimately necessitate the use of a comprehensive code book.

Chest leads, it seems, should be designated by convenient abbreviations of well-known anatomical landmarks which would indicate the approximate location of the principal electrode. This would lead to a clearer visualization of the technic employed by different workers and would enable one to follow the progress of the work initiated by Wolferth and Wood with greater facility. Such a regional anatomical designation would lead, furthermore, to a uniformity of nomenclature expressed in a familiar terminology.

The common sites of location of the principal electrode selected for chest leads at present are: the region of the apex impulse, normally in the fifth space and midclavicular line; the left pectoral region, in the fourth left interspace, about two inches to the left of the midsternal line; and, rarely, the right pectoral region, in the fourth right interspace, about two inches to the right of the midsternal line. These regions may be conveniently designated as the apical, left pectoral, and right pectoral regions, respectively. If the location of the second electrode is chosen and held as a fixed point and if the principal electrode is placed arbitrarily over any one of the regions mentioned above, the resulting lead may then be designated according to the region at which the principal electrode is attached; namely, as an apex lead, a left pectoral lead, or a right pectoral lead; or by the abbreviations, Ap, Lp, and Rp leads, respectively. Such a designation of a chest lead is desirable in that it indicates the location of the principal electrode.

The location of the second electrode, although relatively immaterial, may nevertheless be chosen also with definite purposes in view. We have noted, for instance, that in the conventional chest leads, Leads IV and V of Wolferth and Wood, the auricular complex, P, is generally very shallow and inverted and that at times it is completely absent. We have noted also that, while the location of the second electrode has little influence on the ventricular electrocardiogram, it does influence its amplitude in some degree. The location of the second electrode may therefore be chosen with a view of deriving a tracing which will yield the largest possible deflections in the components of the ventricular portion of the electrocardiogram and which at the same time will include a well-defined auricular P-wave.

*Specific in the sense expressed in footnote on page 801.

The site of application of the second electrode which affords these two features in a chest lead is found to be a most convenient one. It is the right arm or right shoulder. It is a curious and historically interesting fact that as early as 1900 Einthoven and deLint,[14] in search for a lead that would yield the largest possible deflections in their electrocardiogram, came to the conclusion that this requirement was fulfilled best by the right arm apex lead. To quote them verbatim: "Wir legten die Elektroden on diejenigen Stellen des Körpers an, welche die grössten Schwankungen des Potentialunterschiedes zeigten . . . auf der eine Seite der Brustwand nahe by dem Apex Cordis, auf der anderen Seite die rechte Schulter order der rechte Arm."

By the use of a right arm chest lead, then, we can record a tracing which depicts well-defined auricular as well as ventricular complexes and which, at the same time, yields maximal deflections with the galvanometer string at standard sensitivity. These are clearly desirable features in a chest lead. Futhermore, since in a right arm chest lead the right arm electrode is the fixed secondary electrode and the left arm electrode is the one which is employed as the principal electrode, we derive a tracing by this lead which has the added feature of symmetry with the standard leads in that its main deflections correspond in direction with those of the standard leads. This is in keeping with the original intention of Einthoven, who so arranged his circuit for patient and galvanometer that normally all major deflections of his electrical tracings were expressed in positive ordinates. The right arm chest lead has still another and a much desired advantage in that it requires but a single chest electrode. This is a readily recognized convenience in clinical electrocardiography at the bedside.

In summary, then, the right arm chest lead is serviceable as a routine chest lead for clinical use because it embodies the following:

(a) A tracing derived by this lead represents all components of the cardiac cycle, auricular as well as ventricular, in a well-defined form.

(b) All principal deflections in the tracing are maximal for a galvanometer of standard sensitivity.

(c) All principal deflections in the tracing conform in direction with synchronous deflections in the standard leads, thus lending symmetry to the group.

(d) The chest lead is convenient for bedside use in that it requires but a single chest electrode.

Figure 4 shows a group of electrocardiograms taken from a young woman in good health, to illustrate the relative form of the right arm apex (R-Ap) lead as compared with standard leads and several special leads.

It might seem that the introduction of a special lead, the right arm chest lead, would meet with objections on the ground that since the conventional leads have been in use for almost three years, their criteria

being familiar, a change at this time would be inconvenient. But this special lead, if employed, need not necessarily replace all conventional chest leads now in use. In fact, as will be shown, the writer has found it convenient to employ one of the leads of Wolferth and Wood (their Lead V) as a companion chest lead without any change in the arrangement of electrodes. An objection might also be raised on the ground

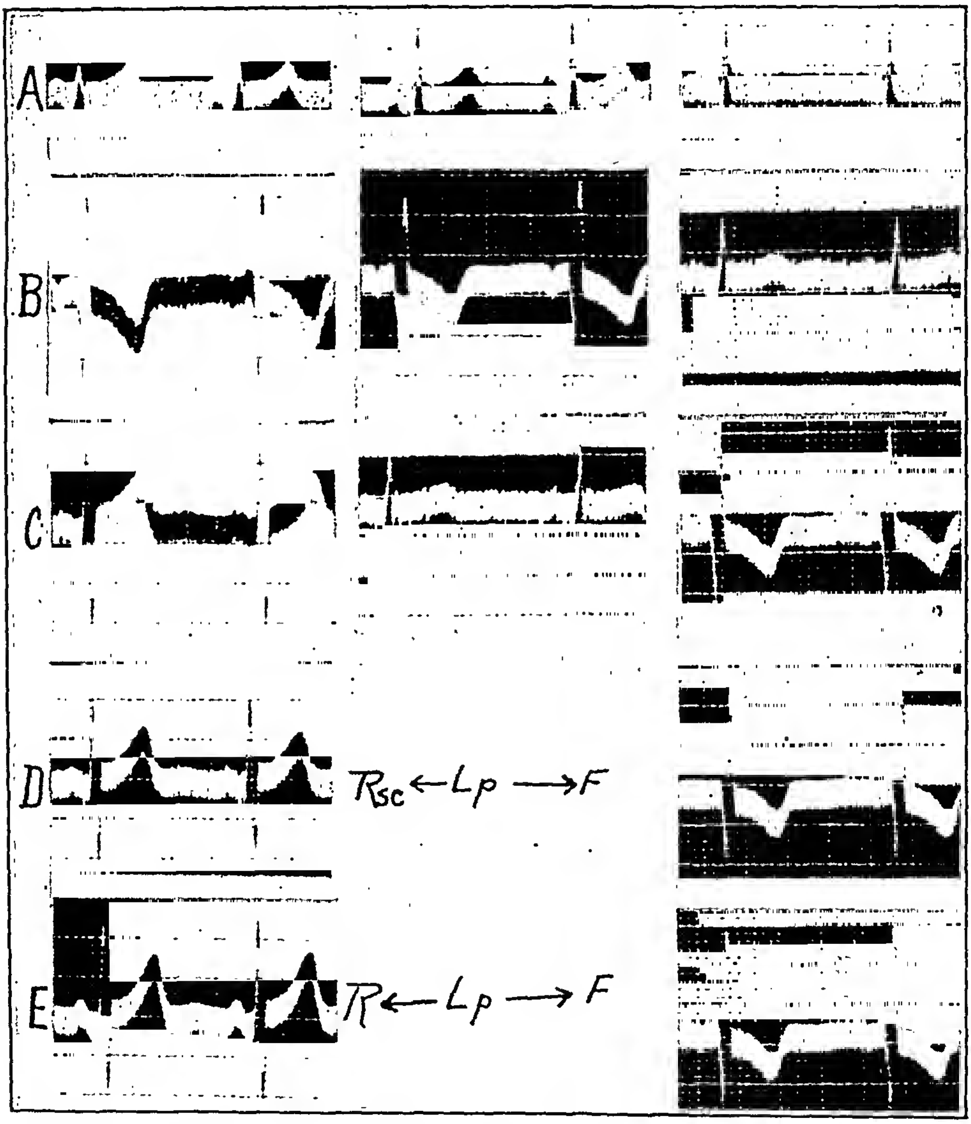


Fig. 4.—Tracings derived by the right arm chest lead and its companion lead, the chest foot lead, as compared with those derived by standard leads and several special chest leads.

In each case the chest electrode was located over the fourth interspace about 2 inches to the left of the midsternal line.

A. Standard Leads I, II, and III.
B. Chest Leads IV, V, and VI.
C. Posteroanterior chest lead; reverse of B.
D. Right scapula chest and chest foot leads.
E. Right arm chest and chest foot leads.

The *right arm chest* lead tracing shows well-defined auricular and ventricular complexes, the components of which correspond in direction with synchronous deflections in the standard leads.

that since Leads IV and V have been recently shown to disclose evidences of residual injury to the anterior surface of the left ventricle (absent Q-wave), this information might be lost by the adoption of the right arm chest lead. Actually, whenever Leads IV and V show absence of Q-waves, the right arm chest lead depicts its equivalent by showing an absence of the R-wave; that is, the ventricular electrocardiogram of the right arm chest lead begins with a conspicuous initial downstroke. This

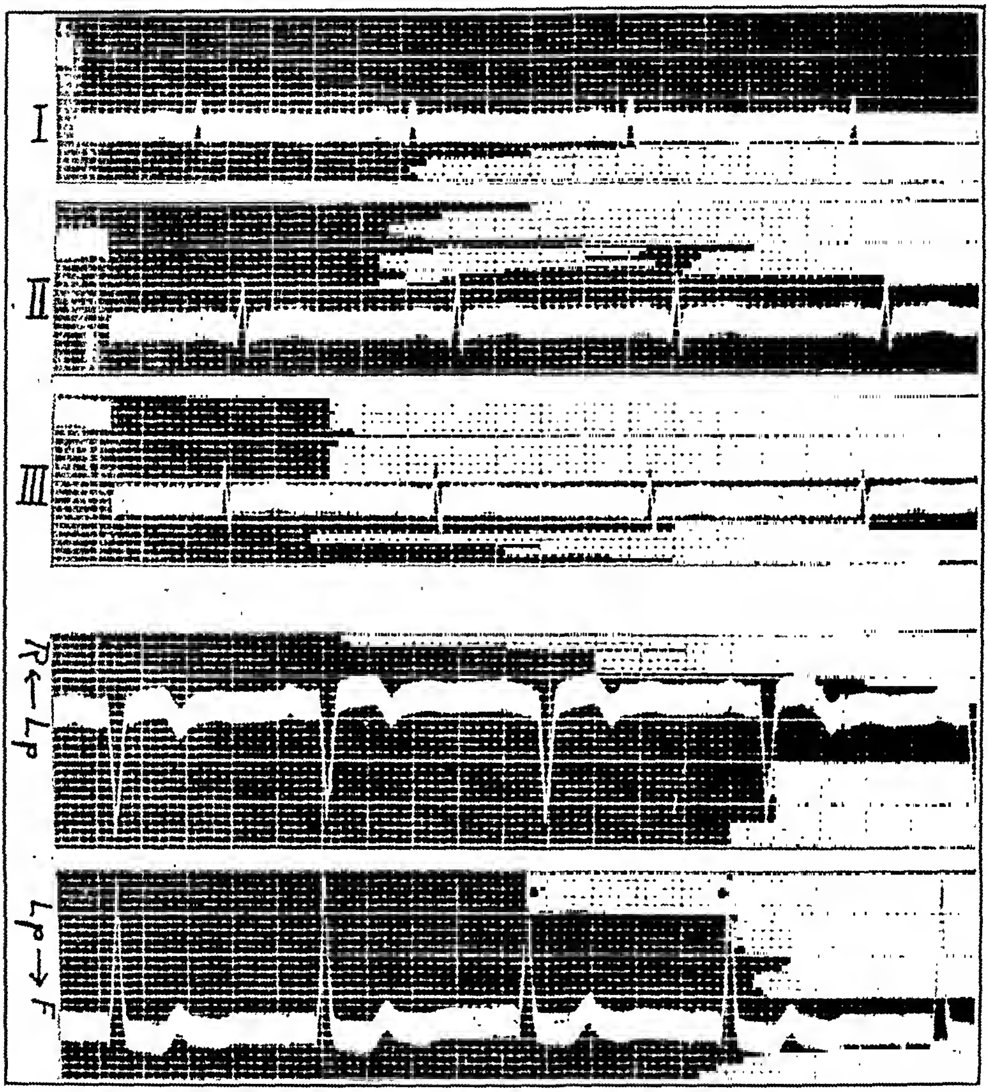


Fig. 5.—Tracings derived by standard leads, the right arm chest lead, and the chest foot lead in a case clinically suggestive of an old injury to the anterior wall of the left ventricle.

The chest foot lead (Lp→F), in conformity with the observations of Wood, Bellet, McMillan, and Wolferth,[11] shows "absence of the Q-wave." The tracing of the right arm chest lead (R←Lp), on the other hand, shows its counterpart, namely, an absent R-wave.

is in conformity with changes often seen in standard Lead I in such cases. It serves as a conspicuous analogue of the Q_1 type standard electrocardiogram, which has now been accepted as an index of previous injury to the anterior portion of the left ventricle. Fig. 5 shows tracings derived

by standard leads, the right arm chest lead, and the chest foot lead (Lead V) in a patient presumed to have an old myocardial injury along the path of the anterior descending branch of the left coronary artery.

The right arm chest lead, therefore, records all the cardinal changes in the ventricular complex which we have learned to regard in conventional chest lead tracings as being indicative of myocardial damage; namely, abnormally directed T-waves and abnormalities in the direction of the initial deflection of the QRS complex. In fact, since these are

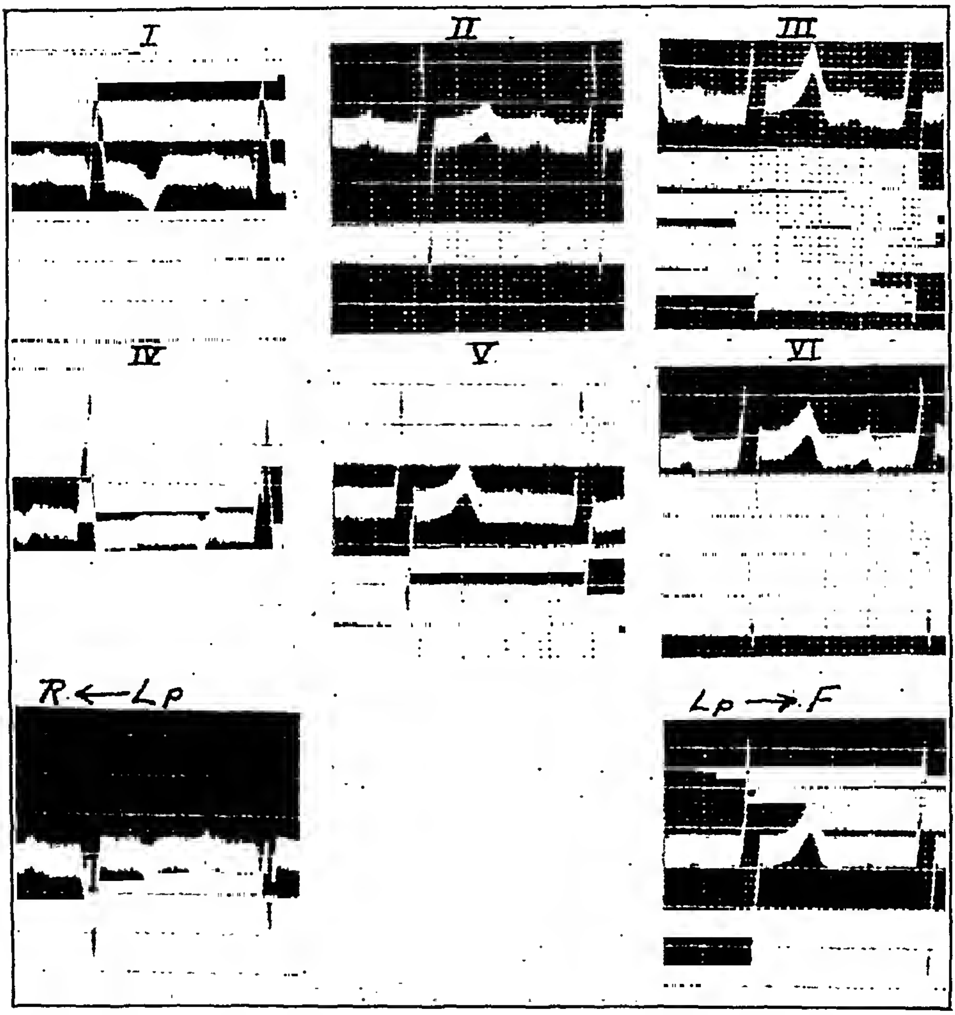


Fig. 6.—Tracings in a case in which Leads IV and V differ markedly in general outline although they both show the same major abnormalities, namely, abnormal T-waves and absent Q-waves.

Right arm chest lead tracings show the equivalent abnormalities, namely, abnormal T-waves and absent R-waves. The R ← Lp lead tracing possesses all characteristics of Lead IV, and the Lp → F lead is identical with Lead V.

the only changes in chest leads which may be deemed of diagnostic value at present, it seems that the right arm chest lead would suffice as a routine chest lead in all cases in which myocardial damage is suspected. It yields all information generally regarded as of diagnostic value in these cases.

It is not claimed, however, that the right arm chest lead is a substitute for all chest leads. The study of chest leads in clinical electrocardiography is of comparatively recent date and may not be restricted. It has been found that certain chest leads which normally resemble each other closely may, nevertheless, differ widely in minor details when derived from persons having chronic fibrotic myocardial lesions. Leads IV and V, for instance, while generally alike in normal hearts and while generally recording the same gross deviations in well-defined myocardial involvement as a result of coronary occlusion, may occasionally differ in details the meaning of which, up to date, is entirely foreign to us. Fig. 6 is an example of such a case. It seems desirable, therefore, for purposes of further study (not necessarily for routine clinical use) that a companion chest foot lead be taken with the right arm chest lead. In the light of our present knowledge this may afford no additional information. However, since we do occasionally encounter cases in which the two chest leads differ in certain details—although, in the main, equally informative with respect to findings which have become familiar—it is desirable that such records be taken and filed for future studies.

The technic of taking the right arm chest lead together with Lead V at the bedside is carried out as follows: The three standard leads are taken. Then the cable of the left arm electrode is detached and is connected to the chest electrode* applied to the region of the cardiac apex (or any other pectoral area). In this position the operator selects on the control board of his instrument, Leads "I" and "III" successively. The first of these (Lead "I") is naturally the right arm chest lead here advocated, and the other (Lead "III") is the companion chest foot lead, which is precisely Lead V of Wolferth and Wood.

Since it is the principal electrode (the one nearest to the heart) which determines the form of the resulting curve, the use of the right arm chest lead was extended in an endeavor to explore different pectoral zones. The principal electrode was applied successively to the right pectoral, left pectoral, and apical regions, the second electrode having been fixed in each case at the right arm. The leads were designated as the right pectoral (Rp), left pectoral (Lp), and apical (Ap) leads, respectively. Each of these leads seems to serve as a distinct source of information. In the right pectoral (Rp) lead the auricular P-wave is conspicuous, especially in cases in which there is clinical evidence of enlargement of the right auricle. In the left pectoral (Lp) lead the terminal ventricular complex, T, stands out most prominently. The apical (Ap) lead, on the other hand, accentuates the initial ventricular complex.

The right pectoral (Rp) lead may be employed to record tracings of auricular activity in cases of auricular fibrillation or other conditions

*There is a wide choice of chest electrodes. Those employed in the cases illustrated in this article were of the self-retaining type, built on the principle of vacuum cups to assure against possible shifting of the principal electrode. The size of the electrode never exceeded 1.5 inches in diameter.

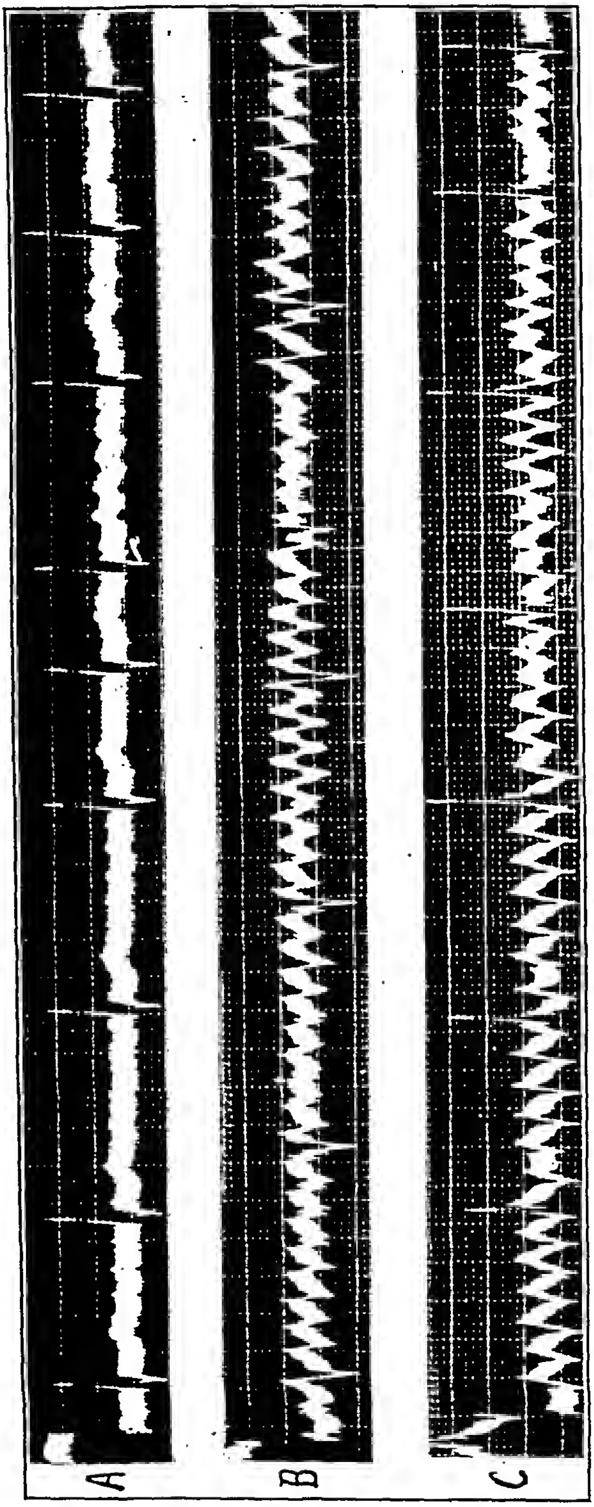


Fig. 7.—A case of auricular fibrillation recorded by *A*, standard lead II; *B*, the right arm right pectoral lead; and *C*, the right pectoral foot lead.

The variations in the form, rate, and rhythm of the auricular waves are brought out conspicuously by both the right arm right pectoral and the right pectoral foot (R ← Rp → F) leads.

in which the right auricle is enlarged. Such a tracing is presented in Fig. 7. In this tracing the auricular waves are remarkably clear, and one can count them accurately over long periods. It also serves to emphasize the profound variations that take place both in rate and contour, in the auricular waves in fibrillation. Another tracing recorded by the right pectoral (Rp) lead is presented in Fig. 8. This tracing shows clearly deciphered auricular P-waves within the different portions of the ventricular complexes, not quite as sharply outlined in the standard tracings.

Fig. 8.—Tracings derived by standard leads and the right arm right pectoral (R ← Rp) lead in a case presenting clinical evidences of an old mitral valvular defect with heart failure. The auricular P-waves are largest in the chest lead tracing, and they are clearly defined even when superimposed on an ectopic ventricular complex.

In the left pectoral (Lp) lead the terminal portion of the ventricular complex is deciphered most conspicuously. This lead therefore seems most serviceable in cases in which standard Lead I is of very low voltage. Clinical cases suggestive of myocardial infarction along the course of the anterior descending branch of the left coronary artery at times yield standard electrocardiograms in which Lead I, the most important lead, although abnormal, may nevertheless be regarded by some as "inconclusive" because of a low amplitude of the T-wave. In such cases the left pectoral (Lp) lead will generally serve to accentuate the terminal

ventricular complex (RS-T and T) with all its abnormal deviations sufficiently to render the tracing acceptable as evidence of the myocardial damage presumed to have taken place. Fig. 9 is a striking example of such a case. The electrocardiograms presented in this figure were recorded shortly after the clinical "coronary episode"—a few hours after. Experience has taught us to regard the shallow standard Lead I in such a case as being abnormal and definitely pointing to the diagnosis of a focal myocardial involvement. Yet, since some may regard it as "inconclusive," the Lp chest lead should accompany the standard electrocardiogram in order to accentuate the RS-T deviation sufficiently to remove all doubt.

The apex (Ap) lead is essentially for the same purpose as the left pectoral (Lp) lead, except that in the former the QRS is somewhat taller and the T-waves not quite as tall as in the latter. The apical

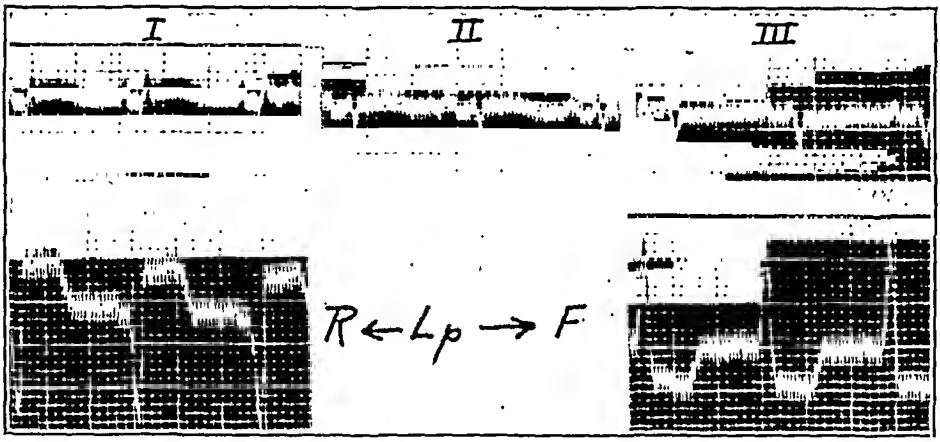
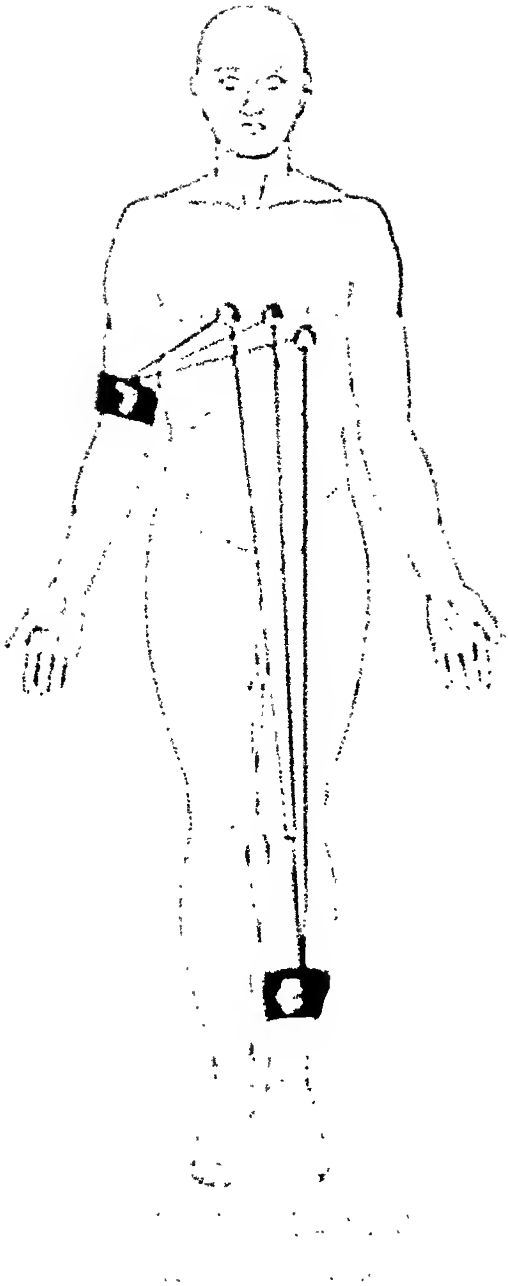


Fig. 9.—Tracings in a case of an acute left coronary occlusion, recorded by standard leads and by the right arm left pectoral and left pectoral foot (R ← Lp → F) leads, taken about six hours after the onset of angina pectoris.

The standard lead tracings are of very low voltage but Leads I and II show a characteristic high take-off of the RS-T segment. The chest leads magnify this deviation sufficiently to remove any doubt that might be occasioned by the low voltage in the standard leads.

application of the principal electrode has been the most common practice in chest leads. Yet for many reasons apex leads are least reliable. In employing this lead, there is usually some element of uncertainty as to whether the operator has really found the point of application of the principal electrode he has sought. The apex impulse, at best, is very elusive. This is particularly true in patients at an age when they are most liable to sustain a coronary occlusion. The chests of persons at middle age are often of the obese and hypersthenic type; their lungs, emphysematous; and their hearts, especially after an acute injury, may be too feeble to produce a palpable impulse. It is likely also that in his desire to locate the apex impulse accurately the operator at times applies the electrode beyond the boundary of the heart. This probably accounts for some of the cases which show marked differences in the chest leads



trode is situated approximately midway between the cardiac apex and the midsternal line.

It seems from the foregoing that, if only a single chest lead is intended to complement the standard leads, the object of the operator being merely to clarify such abnormalities in the electrocardiogram as may appear principally in Lead I (suggestive of anterior surface lesions), the left pectoral (Lp) lead is the chest lead of choice. As has been stated, this lead may be supplemented by its companion tracing, the left pectoral foot, Lead V of the conventional set of chest leads.

However, a single chest lead or, for that matter, a pair of companion chest leads (from the same point on the anterior chest wall), while helpful as an aid to the standard leads, is essentially limited in scope. The information it may yield is limited because a chest lead tracing is an expression of the electrical changes of those structures mainly which are nearest to the principal electrode. This is a singular property of chest leads and, as such, may be utilized to gain wider information. It enables one, even by way of gross plotting, to record electrical changes that emanate from certain structures in excess to those of neighboring structures. This can be accomplished by applying the principal electrode over selected zones beneath which a given structure, whose effects are sought, is presumably situated. Unfortunately, the posterior cardiac surface is not readily accessible for investigation by means of chest leads because it rests on the diaphragm. However, the anterior chest wall affords a ready approach to the study of structures that make up the anterior cardiac surface, namely, the right auricle and the two ventricles.

For a study of the electrical effects of the cardiac chambers that comprise the anterior surface of the heart, the right pectoral, left pectoral, and apical chest leads lend themselves conveniently. It seems desirable, therefore, that these chest leads be employed in electrocardiography either singly or paired with their companion leads, in addition to the standard leads, whenever a more general study of the electrical effects of the heart is intended. The procedure is not particularly time consuming. A diagram in Fig. 10 shows the arrangement of the electrodes for these leads. As has been suggested, they may be designated by convenient abbreviations of anatomical landmarks indicating the position of the electrodes. If employed as single leads, they may be recorded as:

$$R \longleftarrow Rp$$
$$R \longleftarrow Lp$$
$$R \longleftarrow Ap$$

or when employed in pairs, as:

$$R \longleftarrow Rp \longrightarrow F$$
$$R \longleftarrow Lp \longrightarrow F$$
$$R \longleftarrow Ap \longrightarrow F$$

These tabulations show at a glance that the secondary electrodes attached at the right arm and the left foot are fixed and occupy the same positions as in the standard leads; they show also that the principal electrode attached to the left arm cable has an arbitrary location over the anterior chest wall. The arrows indicate the directions of the major components of the electrocardiogram recorded by each lead.

In conclusion it might be added that no matter what form routine chest leads might eventually take, chest leads have apparently found a permanent place in clinical electrocardiography. However, since our present knowledge as to the meaning of chest lead tracings is still limited, it seems incumbent upon us not only to be cautious in our observations but also to be critical in evaluating observations recorded by others. Standard lead tracings are still to be regarded as the more reliable guides in clinical electrocardiography. The early warning of Wolferth and Wood to the effect that the chest lead "does not in any way replace the routine electrocardiogram, but should be used as an adjunct to it" has a significant meaning. In this connection one is impelled to urge that in our present enthusiastic preoccupation with chest leads a parallel study of the standard leads should be persued with unabated diligence.

SUMMARY

The literature on chest leads in clinical electrocardiography is reviewed. This review is accompanied by comments on articles and case reports dealing with the subject.

The early literature appears to be colored by an unwarranted enthusiasm on the subject, leading on the one hand to an overemphasis of the value of chest leads, and on the other to a tendency to underrate the significance of abnormalities in the standard leads.

The conventional chest leads, Leads IV, V, and VI have been examined, and their significant features are discussed.

It is suggested that a chest lead for routine electrocardiography embody the following features: (a) that its tracing record maximal deflections and that it include well-defined auricular as well as ventricular complexes; (b) that its tracing be symmetrical with the standard leads; and (c) that the chest lead require but a single chest electrode.

The right arm chest lead has been found to fulfill these requirements.

Objections are offered to the numerical designation of chest leads. It is suggested that instead chest leads be designated by well-known anatomical landmarks, indicating the location of the principal or chest electrode.

Right pectoral (Rp), left pectoral (Lp), and apical (Ap) leads are suggested as routine chest leads in clinical electrocardiography. In these the right arm attachment used in the standard leads serves as the fixed secondary electrode, and the principal or chest electrode is attached to the left arm cable.

It is concluded that while chest leads have found a permanent place in clinical electrocardiography, standard leads are still to be regarded as the more dependable, and a parallel study of standard lead tracings, particularly with reference to minor deviations, should be persued with at least as much attention as the study of chest leads.

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The American Heart Journal

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Official Organ of the American Heart Association

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Retrospect and Prospect

The appearance of this issue marks the completion of the first ten years of the existence of The American Heart Journal, and the occasion is welcomed as offering an opportunity for the Journal to express to its contributors and subscribers its deep appreciation of their constant, friendly support and cooperation.

By a coincidence this tenth anniversary is to be marked, also, by certain developments in the policy of the Journal by which its scope will be widened and its usefulness, it is believed, much increased.

The recent extraordinarily rapid growth of interest in the peripheral vascular disorders and their study has led to a recognition by the workers in that field of the need of some form of organization and of some central outlet for their contributions.

As the result of recent conferences between a representative group of workers in the field of peripheral vascular disease and the directors of The American Heart Association it has been decided to establish in The American Heart Association a standing committee, or special section, for the study of the peripheral circulation. It is expected that The American Heart Journal will serve as the chief medium for the publications of this group.

The problem of providing space for the anticipated large increase in the volume of material offered to the Journal as the result of this ar-

rangement has been met by the willingness of the publishers to increase the number of issues from six to twelve a year. Beginning, then, in January, 1936, THE AMERICAN HEART JOURNAL will appear monthly instead of bimonthly as heretofore, and the editorial staff will be increased by the addition of Dr. Edgar V. Allen, of Rochester, Minn., to the Advisory Editorial Board and of Dr. Irving S. Wright, of New York City, as Associate Editor.

The increase in the number of issues will require a slight increase in the annual subscription price (from $7.50 to $8.50), but this will be more than offset, it is believed, by the offering of a new "journal membership" which provides both annual membership in The American Heart Association and a year's subscription to the JOURNAL for ten dollars.

In order that the changes planned may begin with a new volume of the JOURNAL it has been decided to continue Volume 10 to include the October and December numbers. For that reason the index, which usually is placed in the August issue, will be held over and published with the December number.

Society Transactions

NEW YORK COMMITTEE ON CARDIAC CLINICS, 1935

THE annual scientific meeting of the New York Committee on Cardiac Clinics was held in New York City on April 23, 1935.

The following are abstracts of papers presented or read by title:

Studies on Circulation Time and Intravenous Pressure. William Benenson, M.D., and Elmer A. Kleefield, M.D.

ABSTRACT

Measurements of intravenous pressure by direct manometry and of circulation time from antecubital vein to tongue by the saccharin method were determined on sixty-seven hospitalized patients with varied illnesses. Cases were tabulated in order of increasing circulation times (8.2 to 48 seconds), with other comparable data. The first thirty-four with times of from 8.2 to 16 seconds are noncardiac and cardiac patients without clinical evidence of insufficiency. Eighteen cases comprise the second group, with circulation times ranging from 17.4 to 24 seconds. These are predominantly patients with severe cardiac disease without congestive failure. The last fifteen cases have times of from 24 to 48 seconds. All are clinically listed as patients with congestive failure.

There was no close correlation between intravenous pressure and cardiac function except that high pressures are encountered in extremely decompensated cardiac patients. In certain cases of congestive hepatomegaly there is a rise of intravenous pressure with palmar pressure on the liver. Saccharin timing shows a close correlation to cardiac function, is of aid in the study of the progress of a heart case, is occasionally helpful in differential diagnosis, and is safe, inexpensive, not unpleasant, and easy to perform.

Studies on the Diuretic Effect of Mercupurin in Man. Arthur C. DeGraff, M.D., J. Ernest Nadler, M.D., and Robert C. Batterman, M.D.

ABSTRACT

Controlled clinical studies were made on the diuretic properties of mercupurin (novurit), a complex mercurial salt having chemically bound to it 3.5 per cent theophylline. Patients with marked congestive heart failure who did not lose weight on complete rest in bed were chosen. Some of these patients had not responded to adequate doses of digitalis. Mercupurin produced a definite diuresis in twenty-two cases. The diuretic effect was increased by the addition of ammonium chloride. In eight cases the action of mercupurin was compared with that of salyrgan. Six of these gave a greater diuresis with mercupurin, and two cases were equivocal. Both salyrgan and mercupurin were studied in three cases by having the patient void every half hour on the days the diuretic was given. The peak of the diuretic effect occurred between the fourth and fifth hour with both drugs, and in each case mercupurin produced the greater diuresis.

When the mercupurin salt free of theophylline was used, the diuresis was less. Evidence submitted indicates that theophylline increases the diuretic effect in

man and lessens the local toxic action of the mercurial salts in animals. Neither mercupurin nor salyrgan caused any increase in the number of red blood cells in the urine or gave any other evidence of toxic effect on kidney.

A New Method of Heart Sound Recording. M. D. Feltenstein, M.D., and Myron M. Schwarzschild.

ABSTRACT

A method is used for recording heart sounds so that the graph agrees with auscultation. This is accomplished by introducing distortion in the electrical system of the recorder in order to stress high frequencies in the same way as the average ear does. All audible sounds are recorded, and no inaudible vibrations are registered. The records are made simultaneously with the electrocardiogram. Because of the smooth base line, timing is accurate. The salient characteristics of normal sounds are: (1) the first sound begins on the down stroke of R and persists from 0.06 to 0.12 second with an average frequency range of 75 to 500 cycles; (2) the second sound begins on the down stroke of T and persists from 0.04 to 0.06 second with an average frequency range of 50 to 350 cycles.

Murmurs are differentiated only by duration and position in the cardiac cycle. Sounds occurring prior to the apex of R are diastolic. Systolic murmurs may be recognized if the apparent first sound lasts more than 0.12 seconds. Split sounds do not include a silent interval and have a total duration within normal limits.

Action Potentials Near the Dorsal Surface of the Human Heart. Frederick H. Howard, M.D.

ABSTRACT

Records have been made by means of an esophageal electrode. While the exact position of this electrode has not yet been determined, it appears to have been placed in positions near the line of junction of the right and left sides of the heart.

The electrocardiogram so recorded is distinctive. Auricular activation is indicated by a brief diphasic deflection (P′), first positive, then negative. There is no P-wave. P′ occurs about 0.03 second after the beginning of impulse formation in the sinus and about 0.12 second before ventricular activation. In two cases in which the P-R interval was prolonged (0.40 second and 0.30 second in standard leads), P′ occurred about 0.10 second after P, suggesting that in some cases of delayed conduction there is a delay between the sinus and the point in the auricle near which the electrode lies. The initial ventricular complex is diphasic, first negative, then positive. It resembles closely that obtained from the precordium near the apex, except for the important difference that the sense of the deflection is reversed.

The Differentiation of Pulmonary and Cardiac Disease: The Evaluation of the Rôle of Each. Arthur M. Master, M.D., Harry L. Jaffe, M.D., and Simon Dack, M.D.

ABSTRACT

Dyspnea, orthopnea, cyanosis, coughing, and signs of congestive heart failure may appear in both cardiac and pulmonary disease. In fifty patients, history, physical examination, fluoroscopy, electrocardiogram, vital capacity, blood velocity, venous pressure, and exercise tolerance tests were utilized. In cardiac disease, precordial pain is likely to be more prominent. Severe cough, particularly with expectoration, is found in lung disease. Cardiac irregularities, such as auricular fibrillation and heart-block, gallop rhythm, and hypertension, indicate cardiac

involvement. The venous pressure is high in right heart failure but normal or low in pulmonary conditions. The circulation time, both arm-to-tongue and arm-to-lung, is normal or shortened in pulmonary disease and delayed in heart failure either right or left. The roentgen ray film and fluoroscopic examination may give evidence of heart and aortic involvement, for example, an enlarged or valvular type of heart, left ventricular hypertrophy, or a dilated or tortuous aorta, etc. In lung disease one may find a small heart or evidence of emphysema. The electrocardiogram may show definite evidence of myocardial involvement. The vital capacity is reduced in both states as is also the quantitative measurement of exercise tolerance. The basal metabolic rate is increased in congestive heart failure and in the presence of dyspnea or cyanosis.

Observations of the Roentgenographic Appearance of the Esophagus in the Diagnosis of Disease of the Heart and Aorta. John B. Schwedel, M.D.

ABSTRACT

The use of a barium-filled esophagus in the diagnosis of heart disease has become widespread enough to warrant a few critical remarks as to its limitations. Enlargement of the left auricle displaces the barium-filled esophagus posteriorly and in the case of associated rotation of the heart, also slightly to the right. The esophagus crosses the arch near its junction with the descending aorta. It is attached here very frequently by dense adhesions so that elongation of the aortic arch associated with various cardiac conditions will displace the barium-filled esophagus posteriorly and to the left. These are seen best in the left anterior oblique (posterior displacement) position and postero-anterior (displacement to left) positions. The displacement due to aortic elongation may simulate that of an enlarged left auricle and must be differentiated from it by noting carefully the course of the esophagus in the postero-anterior view. Occasionally, elongation of the aorta is also associated with enlargement of the left auricle presenting a curve, not only to the left in the postero-anterior view, but also to the right in its lower portion. In certain congenital anomalies there is a deviation of the aorta to a central position or even to a dextro position so that the indentation of the aorta is absent or may appear on the right side of the esophagus.

The Effect of Irregular Rhythms of the Heart on the Minute Volume Output of Blood From the Heart in Human Beings. Harold J. Stewart, M.D., Norman F. Crane, M.D., John E. Deitrick, M.D., and William P. Thompson, M.D.

ABSTRACT

Since there are few reports in the literature concerning the behavior of the heart when subject to abnormal rhythms, tho following studies were undertaken. Measurements of the cardiac output were made by the Grollman acetylene method, of cardiac size from 2-meter x-ray films, of the arm-to-tongue circulation time by the injection of decholin intravenously, and of the venous pressure by direct method. The observations were made with the patients in the basal metabolic state.

1. Two patients suffering from paroxysmal auricular tachycardia and three patients exhibiting paroxysmal auricular fibrillation showed a smaller cardiac output and larger heart size than after reversion to regular cardiac mechanism.

2. In seven patients subject to rapid auricular fibrillation and exhibiting dyspnea and cyanosis, the cardiac output was less, the heart size was larger, the circulation time was longer, and in two instances the venous pressure was higher than after the ventricular rate had been slowed by giving digitalis. Now, when reversion to the normal rhythm occurred, the heart still being under the influence

of digitalis, the heart size either became smaller or remained unchanged, and the cardiac output either became greater or remained unaltered.

3. In two patients subject to permanent complete heart-block, the cardiac output was less than the normal predicted output. In one instance the stroke volume was greater than normal, and in the other less than normal.

It appears that rapid heart rates, whether the ventricles are beating regularly or irregularly, as well as the slow rate of complete heart-block, may be accompanied by a diminished cardiac output. A heart subject to auricular fibrillation in which the ventricular rate is slowed by digitalis may be as effective as a pump as is that same heart after reversion to normal rhythm, the heart still being under the influence of digitalis.

The Treatment of Rheumatic Carditis by Fever. Katherine Dodge, M.D., and Lucy Porter Sutton, M.D.

ABSTRACT

Among the patients with chorea treated at Bellevue Hospital with induced fever, sixteen children had evidence of acute carditis at the time of treatment. In nine all signs of activity had subsided by the end of treatment. In the remaining seven, signs were gone from a week or ten days following the end of the treatment. Because it appeared that the hearts of these children were benefited by induced fever, we are investigating the effects of fever therapy on carditis without chorea. Radiant energy is being used to produce fever.

We have treated two children with subacute bacterial endocarditis with neither benefit nor harm; one child with extremely severe acute carditis accompanied by polyarthritis and chorea, who subsequently improved, but whether as a result of treatment we were unable to say; and five children with subacute carditis, in two of whom the activity of the infection was strikingly and promptly arrested. In the other three improvement followed more slowly. We believe that fever therapy in the treatment of the subacute forms of active carditis merits further investigation and that the presence of certain forms of organic heart disease is not a contraindication to the use of fever therapy in the treatment of other diseases.

Characteristic Variations in Certain Experimental Chest Leads (Multiplane Chest Leads) With Experimentally Produced Myocardial Lesions, Experimental Ventricular Extrasystoles and Bundle-Branch Block. Joseph Weinstein, M.D., and David I. Abramson, M.D.

ABSTRACT

The results obtained with the use of multiplane chest leads in experimentally produced ventricular lesions in the cat and dog are reviewed. The right and left arm lead wires of the electrocardiograph were connected in various combinations to long linear electrodes placed on the chest wall anteriorly and posteriorly, parallel to and beyond the cardiac borders. The lesions were produced on various surfaces of both ventricles by means of an electric cautery. A study of the records obtained in 25 experiments revealed that the standard leads showed RS-T segment alterations in only about 50 per cent of the cases and Lead IV, in 66 per cent. There were instances when both the standard leads and Lead IV remained normal, but in all the experiments two or more of the multiplane chest leads demonstrated the presence of a lesion. It was observed that the position of the posterior or indifferent electrode was important in the detection of experimental myocardial lesions. It was found that three of these chest leads showed characteristic changes which invariably localized the lesion to one or the other ventricle. Further studies demonstrated the value of these chest leads in localization of experimental ventricular extrasystoles and bundle-branch block.

Department of Reviews and Abstracts

Selected Abstracts

Boothby, Walter M., and Rynearson, Edward H.: Increase in Circulation Rate Produced by Exophthalmic Goiter. Arch. Int. Med. 55: 547, 1935.

The circulation rate is increased in exophthalmic goiter. On the average, the greater the intensity of the disease, as measured by the oxygen consumption, the greater is the increase in the circulation rate.

The increase in the circulation rate in patients with exophthalmic goiter who are not treated with iodine, according to the investigations of Liljestrand and Stenstrom, is much greater than that which occurs in normal persons as the result of an increase in oxygen consumption due to work.

The relative increase in the circulation rate for a given increase in oxygen consumption is definitely less in patients who are treated with iodine than in those who have not received iodine. However, even under these conditions the increase in the circulation rate was, on the average, both in these cases and in those of Fullerton and Harrop, slightly greater than that produced in normal persons by a degree of work that caused a similar increase in oxygen consumption.

These facts suggest the hypothesis that in exophthalmic goiter, especially when the patient is not treated with iodine, there is present in the system a peculiar circulatory stimulant that causes a greater increase of the circulation rate than occurs in a normal subject as the result of a corresponding increase in oxygen consumption due to work. In exophthalmic goiter either this peculiar circulatory stimulant is decreased in amount or its effectiveness is lessened by medication with iodine.

Gladstone, Sidney A.: Cardiac Output and Related Functions Under Basal and Postprandial Conditions. Arch. Int. Med. 55: 533, 1935.

The acetylene method was applied in a study of the effect of digestion on the cardiac output in forty-four determinations on twelve subjects, of whom five had normal cardiovascular systems and seven presented some structural or functional abnormality. A source of error in the method of analysis of gases as originally proposed is discussed; a corrective procedure was applied, resulting in a tendency to increase the results for the cardiac output by approximately 3 per cent. As compared with the fasting condition, the effect of digestion on the circulatory system, as observed from one to three hours after taking a mixed meal of moderate size, consists in a slight increase in the systolic pressure and usually a less marked fall in the diastolic pressure, resulting in an increase in the pulse pressure. The cardiac output in the normal subject increased by from 11 to 47 per cent above the value during fasting, with an average increase of 25 per cent. In the abnormal subjects the increments varied by from 2 to 47 per cent, the average increase being 17 per cent. Several atypical responses in the subjects with pathological conditions were noted.

Weiss, Soma, and Ellis, Laurence B.: Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise. Arch. Int. Med. 55: 665, 1935.

The utilization of oxygen and the production of lactic acid in the upper and lower extremities were compared in normal subjects and in patients having heart disease with and without congestive failure.

The average oxygen utilization during rest was essentially the same in the arm and in the leg. In heart disease without congestive failure, the utilization of oxygen during rest was normal in magnitude, but with congestive failure there was a tendency toward an increased peripheral utilization. This is evidence that in congestive failure the blood flow through the extremities is frequently reduced. Edema of the leg was not found to be associated with a relatively or absolutely increased local blood flow.

In the standing posture, the oxygen utilization of the extremities increased both in subjects with normal and in those with diseased cardiovascular systems, as a result, in part at least, of decreased blood flow.

Immediately after exercise the oxygen utilization increased markedly, but it returned to the level during rest within ten minutes. In a patient with heart disease the oxygen content of the femoral venous blood immediately after exercise was as low as 1.1 volumes per cent.

The average resting level of the lactic acid in the extremities was between 12 and 14 mg. for all groups. Immediately after the patients ceased walking, the lactic acid content of the femoral venous blood draining the active muscle more than doubled; it then fell rapidly during the next ten minutes but did not reach the level observed during rest within twenty minutes. The lactic acid content of the venous blood of the inactive arm rose slightly immediately after the exercise, but in ten minutes was similar to that of the leg, as a result of the mixing effect of the circulation. With the increasing severity of circulatory failure, there was a tendency for the femoral lactic acid to rise to a higher level than normal immediately after exercise and to fall more slowly.

With the exception of one case of congenital intraventricular septal defect, the etiology of the heart disease played no rôle in the nature of the peripheral circulatory response.

Certain patients showed marked cardiac disability, i.e., orthopnea, dyspnea, and low vital capacity of the lungs, and yet they had normal venous pressure, no edema, or hepatic enlargement and normal oxygen utilization and lactic acid response. The disability in these patients cannot be explained on the basis of the behavior of the peripheral circulation. When disturbances in the lactic acid production and peripheral circulation occur, they are the result and not the cause of heart failure.

Wilson, May G., Wheeler, George W., and Leask, Marguerite M.: The Relation of Upper Respiratory Infections to Rheumatic Fever in Children. II. Antihemolysin Titres in Respiratory Infections and Their Significance in Rheumatic Fever in Children. J. Clin. Investigation 14: 333, 1935.

There is presented a correlation of the clinical course with the bacteriological and immunological observations in eighty rheumatic subjects observed over a period of twelve to eighteen months.

The antistreptolysin titer for rheumatic subjects during apparent health gave a basal average of 135 units with a range of 25 to 715 units. There was no significant difference in the range of antistreptolysin titer observed for subjects during apparent health and during respiratory and rheumatic infection. A com-

parison of the antistreptolysin titers of inactive rheumatic subjects during respiratory and "streptococcal" respiratory infections showed a higher average titer and greater rise in titer for subjects experiencing respiratory infection unassociated with hemolytic streptococci in the pharyngeal flora. Two-thirds of the subjects experiencing rheumatic activity unassociated with respiratory infections did not exhibit a rise in antistreptolysin titer.

The antistreptolysin titer of active rheumatic subjects experiencing respiratory and "streptococcal" respiratory infections was similar to that observed for inactive rheumatic subjects experiencing these infections.

Following respiratory infections the antistreptolysin curve was characterized by a steplike elevation within one to three weeks of the onset, rising to a peak and falling by lysis within one or two months on remaining plateaulike at intermediate levels for longer periods, showing successive peaks following repeated respiratory infections.

The rise of the level of antistreptolysin in the serum following respiratory infections seemed directly related to the extent of the local and constitutional symptoms irrespective of the presence of hemolytic streptococci in the pharyngeal flora.

The antistreptolysin curves observed in subjects who developed respiratory infection simultaneously with, or during, rheumatic activity were similar to those described in subjects experiencing respiratory infections alone and bore no relation to the clinical course of rheumatic activity.

These observations do not support the assumption that a rise in the antistreptolysin titer of the serum is conclusive evidence of streptococcal respiratory infection. A rise in the antistreptolysin titer is not a necessary accompaniment of rheumatic fever in children.

McIntosh, Rustin, and Wood, Charles L.: Rheumatic Infections Occurring in the First Three Years of Life. Am. J. Dis. Child. 49: 835, 1935.

From the records of the Babies Hospital covering a period of about twenty-five years, a group of twenty-four cases has been selected in all of which the disease appears to have begun before the age of three years and in which the evidence warrants the diagnosis of rheumatic infection. Six cases in which autopsy was performed are briefly presented.

The incidence of rheumatic infection in subjects under three years of age is probably greater than is generally recognized. History, symptoms, physical signs, and laboratory data in these cases are variable, and the clinical picture is more often that of general infection than that of a specific disease entity.

The outstanding feature of rheumatic infection manifest during the first three years of life is cardiac damage. In this series 96 per cent of the children exhibited either clinically or pathologically rheumatic heart disease.

Wheeler, George W., Wilson, May G., and Leask, Marguerite M.: The Relation of Upper Respiratory Infections to Rheumatic Fever in Children. III. The Seasonal Bacterial Flora of the Throat in Rheumatic and Non-Rheumatic Children. J. Clin. Investigation 14: 345, 1935.

The data presented are based on a twelve-month study of 4,867 throat cultures from 123 rheumatic children and 1,231 cultures from 109 nonrheumatic children.

In addition to the basic flora of the throat, which is relatively constant for each individual, transient invaders are frequently found and tend to show their maximum incidence at well-defined seasons of the year. The seasonal incidence of various organisms in the pharyngeal flora must be considered in evaluating their possible etiological significance.

A comparison of throat cultures from rheumatic and nonrheumatic children shows no significant difference in the frequency or time of appearance of hemolytic streptococci in the throat. There was no noteworthy difference in the incidence of hemolytic streptococci in the throat during apparent health, upper respiratory infection, or rheumatic activity.

These findings do not suggest any definite relationship between hemolytic streptococci in the throat and rheumatic fever.

McGinn, Sylvester, and White, Paul D.: Acute Cor Pulmonale Resulting From Pulmonary Embolism. J. A. M. A. **104**: 1473, 1935.

Case histories of nine patients with the acute cor pulmonale secondary to pulmonary embolism are presented, accompanied by electrocardiographic studies in seven.

The symptoms and signs of extensive pulmonary embolism are variable, but predominating at first are those of shock—namely, collapse, pallor, sweating, apprehension, and a fall in blood pressure—followed by reaction to the infraction itself—namely, fever and elevation of the pulse and respiratory rates. None of these cases showed acute chest pain in the absence of pleural involvement, but most of the patients complained of substernal oppression and suffocation. Respiratory distress was marked in all cases.

If the state of shock from extensive pulmonary embolism is not too great, or after it has largely cleared, there may be found signs indicative of the secondary effect of the pulmonary embolism on the heart itself: that is, the acute cor pulmonale (dilatation of the right chambers) attended by pulmonary artery dilatation. Auscultation in these cases frequently showed accentuation of the pulmonary second sound, gallop rhythm, heard best in and just below the pulmonary valve region, and in two cases a ''pericardial'' friction rub with maximal intensity in the region of the second, third, and fourth interspaces. Cyanosis and engorgement of the neck veins were common manifestations at some time during the attack. These changes remained for only a short period in some of the cases. Pleural friction rubs were heard frequenfly.

Electrocardiograms taken soon after the occurrence of the pulmonary embolism showed similar changes in five of these patients, and, in two others taken some time after the attack, they had some of the characteristics, although they were less definite. The changes that appear significant are the presence of a Q-wave and late inversion of the T-wave in Lead III, the rather low origin of the T-wave with a gradual staircase ascent of the ST interval in Lead II, a prominent S-wave and a slightly low origin of the T-wave in Lead I and an upright T-wave (with inverted P and QRS waves) in Lead IV. In none of the cases was left axis deviation present at the time of the acute episode, whereas the tracings of two patients showed definite right axis deviation.

Electrocardiograms of two patients taken after recovery showed a complete disappearance of the changes already mentioned, and in a third patient there was almost a complete disappearance of abnormalities in a record taken forty-eight hours after the attack and twenty-seven hours after the first electrocardiogram. All three of these cases showed a change in the axis deviation; one had a prolonged P-R interval and in one case in Lead IV, the T-wave was reverting to normal (inverted). Follow-up studies indicate that the electrocardiographic changes are temporary and may disappear within forty-eight hours after the attack of pulmonary embolism.

It is probable that the changes observed clinically and the electrocardiographic variations in cases showing the acute cor pulmonale consequent to pulmonary embolism are due in large part to dilatation and partial failure of the chambers of the right side of the heart.

Magee, H. Ross, and Smith, Harry L.: Auricular Fibrillation in Hyperthyroidism. Am. J. M. Sc. **189:** 683, 1935.

Subjected to the effects of hyperthyroidism, old patients are prone to have auricular fibrillation; young patients, to maintain normal cardiac rhythm. The increased incidence of auricular fibrillation among older patients with hyperthyroidism is only partially attributable to the frequent occurrence of coronary sclerosis and hypertension after the age of forty. Advanced age itself, although unaccompanied by these processes, determines an increased susceptibility of the heart to auricular fibrillation and adds to the likelihood of its becoming decompensated under the stress of hyperthyroidism.

Among 210 cases of auricular fibrillation associated with hyperthyroidism, cardiac enlargement occurred in 79, in 35 of which there was no evidence of hypertension or of preexisting cardiac disease. In the same group of cases of auricular fibrillation, cardiac decompensation was present in 62; in 29 of these, hyperthyroidism was the only cause found for the cardiac decompensation. In only 2 cases did cardiac enlargement or decompensation afflict patients under forty years of age.

Auricular fibrillation resulting from hyperthyroidism is more often transient or intermittent than prolonged or continuous, especially when not accompanied by serious myocardial injury. The arrhythmia often develops, for the first time, during the immediate postoperative period, in which case it ceases spontaneously within a few hours to a few days. Even when cardiac injury has occurred, the fibrillation of the auricles is frequently replaced by normal sinus rhythm when the heart has been relieved of the strain of hyperthyroidism.

Hyperfunctioning adenomatous goiter results in auricular fibrillation and other signs of myocardial insufficiency more often than does exophthalmic goiter. The longer duration of hyperthyroidism in adenomatous goiter is a less important factor in producing the higher incidence of myocardial injury in this disease. Advanced age seems a much more important factor than duration or intensity of symptoms in determining the incidence of auricular fibrillation and myocardial insufficiency of patients with hyperthyroidism.

LaPlace, L. B.: Observations on the Effect of an Arteriovenous Fistula on the Human Circulation. Am. J. M. Sc. **189:** 497, 1935.

A case of traumatic femoral arteriovenous fistula is reported together with observations made with the fistula open, during external compression of the fistula, and after successful surgical repair. Significant changes in the cardiovascular system are described.

The inconstant relationship between the characteristic rise of blood pressure and slowing of the pulse rate on occlusion of the fistula leads to the conclusion that the bradycardiac reaction is not due exclusively to blood pressure changes.

The basal minute volume of the heart was increased 24 per cent by the fistula, but even in the presence of the increased output there was evidence of a relatively diminished capillary blood flow.

In the standing posture compression of the fistula caused a conspicuous increase in translucency of the lung fields as seen fluoroscopically, indicating a marked decrease in the blood content of the lungs.

The area of the silhouette and the transverse diameter of the heart were reduced by 45 per cent following treatment. It is concluded that the cardiac enlargement was due, as Lewis and Drury suggest, to a relatively inadequate coronary blood flow.

It is suggested that the total ablation of the thyroid in cases of coronary insufficiency may be of direct benefit to cardiac function in a manner analogous to the effect of closure of an arteriovenous fistula.

Quirno, Norberto, and Cobo, Jorge Lavalle: Capillaroscopy in States of Acrocyanosis. Rev. argent. de cardiol. **1:** 470, 1935.

As the result of capillary studies in patients suffering from acrocyanosis, the following characteristics were established: cyanotic fundus; stretching; dilatation and tortuosity of the loops, particularly of the venous branch; dilatation of the veins of the subpapillar plexus; very slow blood current and dark blood. The direct action of cold and warm water tests on capillaries, as well as the vasoconstricting effect of pituitary extract and vasoparalyzing effect of histamine, were observed. Different theories are suggested to explain the etiology of this vasomotor syndrome. It is believed that the alteration is due to a low tonus of the capillary venous system. The constricting effect of pituitary extract on capillaries suggests its use in cases of acrocyanosis.

De Takáts, Géza: Peripheral Vascular Disease. Its Significance for General Practitioners and Specialists. J. A. M. A. **104:** 1463, 1935.

This brief survey of the principles of examination, diagnosis, and management of peripheral vascular disease should focus some attention on these common and other significant disorders of peripheral circulation. Most of such material is primarily in the hands of the general practitioner. Some of them will complicate or obscure the problems of other specialties. The more intensive study of these peripheral circulatory disturbances will lead to earlier and better therapeutic results.

There is a brief discussion of methods of examining the peripheral pulse, skin temperature, posture, changes of color, cutaneous histamine reaction, blood pressure measurements, reflex dilatation to heat, and certain other methods.

Cohen, Alfred E., and Lewis, William H.: Lobar Pneumonia and Digitalis. Am. J. M. Sc. **189:** 457, 1935.

An analysis of 1,456 cases of lobar pneumonia observed in the Hospital of the Rockefeller Institute has been undertaken. The patients were admitted over a period of twenty-one years, from 1911 to 1932. An effort was made to ascertain what influence the action of digitalis has on the course of this disease. Its action, in favorable cases, in which auricular fibrillation and auricular flutter occur, appears to be beneficial.

The outcome in lobar pneumonia depends on the severity of the disease, which in turn depends especially on the presence of bacteriemia, the number of pulmonary lobes involved, and the existence of complications.

It is not certain whether the action of digitalis precipitates the occurrence of auricular fibrillation. If it does so, the number of cases is small, especially in the earlier decades.

The proximity of death does not determine the onset of auricular fibrillation. Even when it was present, it ceased in ten of eighteen cases before death.

Heart-block did not occur during the febrile period of lobar pneumonia except in those patients to whom a sufficient amount of digitalis was given to bring it about.

Graybiel, Ashton, and White, Paul D.: Diseases of the Heart: A Review of Contributions Made During 1934. Arch. Int. Med. 55: 842, 1935.

This review is introduced with the following statements:

There has not been a major contribution to the knowledge of heart disease during 1934. Minor advances have been made, however, and some recent gains consolidated. This review does not include all that has been done; it suffices merely to indicate certain trends and to cite some of the more interesting publications. While a few of the reports seem more wonderful than probable, an especially critical attitude has been avoided because the newness of the work prevents conclusion.

Bohning, A., and Katz, L. N.: The Four-Lead Electrocardiogram in Coronary Sclerosis. Am. J. M. Sc. 189: 833, 1935.

A total of 508 electrocardiograms taken with a Lead IV have been analyzed and the data tabulated and summarized. Two hundred were from patients clinically diagnosed to have coronary sclerosis, 50 from patients suspected of having coronary sclerosis but without definite symptoms, 100 from patients with suspected cardiac disease, 25 from individuals with normal hearts, and 133 from patients known to have other types of organic heart disease.

It was found that patients with coronary sclerosis showed abnormalities in Lead IV more often than any of the control groups.

The abnormalities in Lead IV in the patients with coronary sclerosis were almost always associated with abnormal findings in the conventional three leads, but the deviations were usually more striking in Lead IV.

Patients with coronary sclerosis having clinical evidence of myocardial incompetence showed abnormalities in Lead IV more often than patients without such myocardial incompetence.

The four major types of abnormal Lead IV found in patients with coronary sclerosis are described. They are the positive QRS_4 type (the most common), the negative QRS_4 type, the positive and diphasic T_4 type, and the deeply negative T_4 type.

The value of Lead IV in determining the status of the coronary circulation was confirmed by postmortem examination in seven cases of coronary sclerosis.

Serial four-lead electrocardiograms were obtained in 56 of the 200 patients with coronary sclerosis covering a period of from four months to two years or more. Analysis of these records and, in addition, those obtained on patients with recent coronary occlusion and other conditions showed the value of serial electrocardiograms in evaluating the state of the coronary circulation. This is particularly important because of the paucity of precise clinical evidence in a large number of such patients.

If records obtained in patients suffering from acute infectious processes, those taken on moribund patients, and those taken on patients given large doses of digitalis are excluded, then one can determine from serial four-lead electrocardiograms whether the coronary insufficiency is: (1) an acute transitory coronary insufficiency, i.e., angina pectoris, nocturnal dyspnea, cardiac asthma, or its equivalent; (2) a subacute sclerotis with myocardial infarction; (3) a chronic nonprogressive coronary insufficiency; or (4) a chronic progressive coronary insufficiency. This functional classification should prove as useful in evaluating the clinical course of the patients as the anatomical and etiological classifications.

This study emphasizes the importance of taking serial four-lead electrocardiograms in all patients suspected of having coronary disease in estimating the degree of insufficiency of the coronary circulation and the rate of its progress.

Schwab, Edward H., and Herrmann, George: Alterations of the Electrocardiogram in Diseases of the Pericardium. Arch. Int. Med. 55: 917, 1935.

Seven cases of pericardial disease of various types are presented with abstracts of the clinical histories, complete physical and pertinent laboratory data, and serial electrocardiographic studies.

A complete review of the available literature on the subject has been attempted.

The similarity of the deviations in the RS-T sector in cases of pericardial effusion to those occurring in cases of coronary thrombosis with infarction is reiterated.

Attention is directed to the previously unmentioned but significant inversions of the T-wave which follow the changes in the RS-T segment in cases of excess fluid in the pericardial sac following reabsorption, thus continuing the electrocardiographic analogy between pericardial effusion and cardiac infarction.

The occurrence of progressive changes in the T-wave in acute fibrinous pericarditis without an accompanying effusion and without preceding abnormalities in the RS-T segment is emphasized.

An evaluation of the electrocardiographic differences between pericardial disease and cardiac infarction is presented. The absence of the development of significant abnormalities of the Q-wave in pericardial pathological processes is stressed. No information of differential diagnostic value is apparently to be derived from the use of Lead IV.

Some theories as to the mechanisms operative in the production of the types of electrocardiographic changes encountered, based on the clinical and experimental studies, are brought forth. The changes in the RS-T sector are apparently the result of ischemia of the cardiac muscle, and the progressive and retrogressive changes in the T-wave seem to be associated with organization and repair of the process in the epicardium and subepicardial myocardium.

Tennant, Robert, and Wiggers, Carl J.: The Effect of Coronary Occlusion on Myocardial Contraction. Am. J. Physiol. 112: 351, 1935.

An optical myograph suitable for recording localized contractions from a ventricular surface and a technic for its correct application are described.

Normal myograms recorded simultaneously with aortic or ventricular pressure curves, though slightly deformed by oscillations during the isometric contraction and relaxation phases, clearly show the natural shortening which occurs during ventricular ejection and the lengthening which follows isometric relaxation.

Occlusion of a main coronary branch is followed by an evoluting series of myographic changes which indicate progressive enfeeblement of contraction to the extent that approximately within a minute the area stretches during isometric contraction, remains stretched during systolic ejection, and shortens quickly during isometric relaxation; in short, the myogram is completely inverted. Similar changes in contraction of the right ventricle occur following ligation of the right coronary artery. These observations demonstrate convincingly the functional inadequacy of described collateral circulation in normal hearts.

Reestablishment of the normal blood supply is followed by a reversed series of myographic changes with restoration of normal vigorous contractions provided that the period of ischemia is not too long in duration.

Failure of shortening is due to enfeeblement or abrogation of contraction and not to failure of impulses to reach the areas involved or to excite them.

The oxygen requirements for maintaining efficient contractions in the normally working heart are high as evidenced by the failure to maintain efficient contractions when an area is being perfused with highly oxygenated Locke's solution.

The observations supply tangible proof for the correctness of Orias' hypothesis that coronary occlusion produces an early abbreviation of total ventricular systole

with little or no decline of systolic pressure through a progressive decrease in amplitude and duration of contraction in the ischemic area. The results suggest further that the tendency for development of hypodynamic ventricular beats following coronary occlusion may not necessarily be due to fatigue of the remaining contracting fibers, but can be explained by loss of pressure in expanding the regions in which contractions are enfeebled or absent.

Several clinical implications of the results are briefly discussed.

Brown, Morton G.: The Relationship of Coronary Arteriosclerosis to Auricular Fibrillation With Special Reference to the Term "Arteriosclerotic Heart Disease." New England J. Med. **212:** 963, 1935.

An analysis was made of all cases coming to postmortem examination at the Peter Bent Brigham Hospital in the years 1913 to 1933 that showed auricular fibrillation exclusive of those with known rheumatic valvular disease. Particular attention was paid to the relation between this irregularity and disease of the coronary arteries. There were 119 cases, 91 with permanent and 28 with transient auricular fibrillation.

Hypertension was an etiological factor in 79.3 per cent of the cases with permanent fibrillation and in 86.5 per cent of the cases with transient fibrillation. Significant disease of the coronary arteries, although fairly frequent among those with hypertension, was not common as the sole factor in the development of permanent auricular fibrillation. Angina pectoris and coronary thrombosis were comparatively raro in patients who had had auricular fibrillation. There was a group of nine cases classified as of undetermined etiology which had no significant coronary artery disease or known previous hypertension.

There were nine cases showing other forms of heart disease, such as pericarditis and unrecognized stenosis of one of the valves. Finally there were additional fifteen instances with auricular fibrillation with no disease of the heart, five of which had hyperthyroidism.

Males predominated over females in a proportion of 2 to 1, and the ages ranged from thirty-nine to eighty-nine years with the majority between the years fifty to seventy. The heart weight was greater in the males and in those with permanent fibrillation than in the females or in those with transient fibrillation. Although congestive failure was the most common cause of death, it is of interest that pulmonary infarction was quite frequent and renal insufficiency rare.

Evidence is presented that marked peripheral sclerosis of itself need be no indication that the coronary arteries are sclerosed nor that the efficiency of the heart is in any way altered. From this it is therefore suggested that the term "arteriosclerotic heart disease" should be given up entirely or clarified in its expression.

Maynard, E. P., Jr., Curran, J. A., Rosen, I. T., Williamson, C. G., and Lingg, Claire: Cardiovascular Syphilis: Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis. Arch. Int. Med. **55:** 873, 1935.

Present investigation was planned in order to study the natural history of syphilitic infection in relation to its effect on the cardiovascular system. Three hundred and forty-six patients with syphilis were studied. One hundred and forty-five (41.9 per cent) showed positive evidence of cardiovascular syphilis.

There were fourteen adult patients with congenital syphilis. In none of these was evidence of syphilis of the heart or aorta found.

The date of occurrence of the primary lesion was known in about half of the patients (55 per cent). The average age at which infection occurred was twenty-

six years. In a quarter of the patients studied, the chancre appeared before the age of twenty-one years.

One-fourth came for examination within one year, and one-half within ten years, after the occurrence of the initial lesion.

Evidence of cardiovascular syphilis was found within ten years after the appearance of the chancre in one-fourth of the cases, although the average interval from infection to the discovery of heart disease was twenty years. Symptoms were somewhat slower in making their appearance. One-fourth of the patients complained of symptoms within fourteen years after the development of the primary lesion. The average interval before symptoms occurred was twenty years.

Evidence of cardiovascular syphilis was found within the first three years after the appearance of the chancre in 8 patients (14 per cent). One in the entire group complained of symptoms referable to the heart.

Of twenty-one persons who were not examined until four to nine years after primary infection, six (28.6 per cent) revealed the presence of cardiovascular syphilis. Two of these suffered from aortic insufficiency, and one, from aneurysm. Symptoms were present in three of the six.

Among thirty-seven persons who were not examined until ten to nineteen years after the primary lesion, twenty-one (56.8 per cent) exhibited evidence of cardiovascular syphilis. Symptoms appeared in 51.3 per cent of these. Heart failure occurred in two patients, in both of whom aneurysm or aortic insufficiency was present.

In a group first observed from twenty to twenty-nine years after infection, 77.8 per cent exhibited signs of syphilitic heart disease; 40 per cent presented either aortic insufficiency or aneurysm. Symptoms were present in 78 per cent.

Of seventeen persons who were first examined thirty or more years after infection, fifteen revealed the presence of cardiovascular syphilis, and seven either the presence of aortic insufficiency or of aneurysm. Three quarters of them complained of cardiac symptoms.

Heart failure occurred only in those patients in whom aortic insufficiency, aneurysm, or involvement of a coronary artery developed.

There were significant changes in the electrocardiograms within ten years after the appearance of the chancre in only 10.4 per cent. No changes were found that could be considered characteristic of the condition.

A case is reported of a patient whose condition was diagnosed as syphilitic disease of a coronary artery, who died within two years after the occurrence of the chancre. Postmortem examination confirmed the diagnosis.

From this study the following conclusions were drawn:

Syphilis of the aorta can be recognized much earlier now than it could be in the past. In order to discover its presence, it is necessary that every syphilitic patient be examined regularly by methods used in making a diagnosis of cardiovascular disease. These examinations should be repeated once in six months or once a year.

Roentgenograms and fluoroscopic examination provide the most reliable means of deciding whether abnormality of the aorta is present in early syphilis.

Heart failure occurs only in those patients in whom syphilitic involvement has passed beyond the stage of simple aortitis. In the patients studied, myocardial failure appeared only after the development of aortic insufficiency, aneurysm, or narrowing of the coronary arteries. Multiple gummas may be regarded as a cause of heart failure, but this condition was not encountered in this study. It is well known that these four manifestations are late lesions. Symptoms of heart failure usually prompt patients to seek relief in clinics for cardiac disease. Since these tend to occur late in cardiovascular syphilis and since no special routine effort has been made in the past to examine syphilitic patients for evidence of cardiovascular

disease, the discovery of aortitis has been delayed. It is probably not true that syphilitic aortitis is a late lesion occurring, on the average, twenty years after the occurrence of the chancre. The authors' opinion is that involvement of the aorta begins soon after the chancre has appeared and that in the past discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination.

Schwarz, Herman, and Leader, Sidney: Latent Cardiac Complications Following Sydenham's Chorea. Am. J. Dis. Child. 49: 952, 1935.

Seventy-five cases of so-called "pure" chorea were observed for from one to twelve years for evidence of cardiac involvement. The term "pure" chorea was used for the cases of chorea in which no other manifestations of rheumatism were noted clinically.

The longer the period of observation after the first attack of chorea, the higher was the percentage of cardiac involvement found; it apparently reached 100 per cent after seven or eight years, although the number of cases studied is too small to permit a definite statement. The signs of cardiac involvement developed insidiously, without recognizable attacks of rheumatic fever and in some cases without further attacks of chorea. In this series aortic murmurs, pericarditis, and subcutaneous nodules were never encountered.

It seems probable that what is said of rheumatic fever may also be said of chorea: "The heart is always involved." This probable cardiac involvement is added evidence that Sydenham's chorea is of rheumatic origin.

Ferris, Eugene B., Jr., and Myers, Walter K.: Initial Attacks of Rheumatic Fever in Patients Over Sixty Years of Age. Arch. Int. Med. 55: 809, 1935.

Six cases of patients over sixty years of age with first attacks of rheumatic fever are reported. In three cases the diagnosis was confirmed at autopsy.

The course of the disease is similar to that in younger persons, except that the manifestations in the joints are possibly less intense and more persistent.

In older patients with polyarthritis, rheumatic fever should be considered as a diagnostic possibility.

McIntosh, Rustin, and Wood, Charles L.: Rheumatic Infections Occurring in the First Three Years of Life. Am. J. Dis. Child. 49: 835, 1935.

The authors have selected from the records of the Babies Hospital, covering a period of about twenty-five years, a group of twenty-four cases in all of which the disease appears to have begun before the age of three years and in which the evidence warrants the diagnosis of rheumatic infection. This series and others illustrate that rheumatic infection is rare, although not exceptional, before the age of three years. The incidence is probably greater than is generally recognized.

The history, symptoms, physical signs, and laboratory data in these cases are variable, and the clinical history is more often that of general infection than that of a specific disease entity. The outstanding feature of rheumatic infection manifest during the first three years of life is cardiac damage. In this series 96 per cent of the children exhibited, either clinically or pathologically, rheumatic heart disease. Six cases in which autopsy was performed are briefly presented.

King, Robert L.: Heart Disease in the Pacific Northwest. Northwest Med. 34: 154, 1935.

Heart disease ranks first as a cause of death in the states of the Pacific Northwest; furthermore, there has been a progressive rise in the mortality rate from this

cause, paralleling that of the United States Registration Area. Morbidity statistics compiled from hospital records are not reliable.

An analysis of the records of 556 private patients suffering from organic heart disease was made to determine the relative incidence of the various etiological factors, as well as their associated abnormalities. From this study hypertension (49.4 per cent), arteriosclerosis (20.3 per cent), and rheumatic fever (20 per cent) were found to represent the etiological factors in 90 per cent of the cases. Other less frequent factors were syphilis, thyrotoxicosis, and congenital maldevelopments. Acute rheumatic fever was rare, and syphilis was not a common cause of heart disease, findings which correspond to similar groups of private patients. Subacute bacterial endocarditis occurred in 2 per cent of the patients.

Katz, Louis N., Mayne, Walter, and Weinstein, William: Cardiac Pain: Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels. Arch. Int. Med. **55**: 760, 1935.

The observation of earlier workers is confirmed that occlusion of the coronary vessels and the surrounding tissue in the unanesthetized dog gives rise to an effective response resembling an anginal attack. The response from this procedure is similar to that obtained on compressing a superficial somatic sensory nerve, save for the inability of the animal to locate the site of irritation.

The results show that this response is due not to the occlusion of the coronary artery, but to stimulation of afferent fibers located in the nerve plexus surrounding the vessels. The evidence for this is:

1. Occlusion of a carefully isolated strip of the coronary artery caused no response, but a definite response was obtained when the undissected coronary vessels above and below this point were compressed.

2. Destruction of the nerve plexus with phenol and alcohol abolished the response to compression, but the response was still positive when a region above the phenolized area was stimulated.

3. Complete preliminary occlusion of the carefully isolated coronary artery did not prevent a positive response to compression above or below this point.

4. Pericardial tamponade following bleeding from a ruptured coronary artery caused syncope but no ''anginal'' response.

5. Positive affective responses occur only when the region about the coronary vessels is compressed. The rest of the myocardium and epicardium is insensitive to stimulation by pressure.

It is concluded that ischemia of the myocardium is at most one of many mechanisms operating on the nerve endings and nerve fibers which may give rise to anginal attacks.

Goldsmith, Grace A., Brown, George E.: Pain in Thrombo-Angiitis Obliterans. Am. J. M. Sc. **189**: 819, 1935.

There are seven distinct recognizable types of pain in thromboangiitis obliterans. The two major factors involved in the production of pain are ischemia and inflammation. The types of pain observed in arteriosclerosis obliterans are similar to those in thromboangiitis obliterans, with the exception that pain resulting from phlebitis and arteritis is absent.

Intermittent claudication was the initial symptom in more than 90 per cent of the cases in this series. The recognition of the arterial basis of this symptom is of crucial importance, as avoidance of ulcers and gangrene and preservation of limbs depend largely on early appreciation of the circulatory impairment. The presence

or absence of pulsations in the peripheral arteries should be determined in any case in which pain in the extremities is a prominent feature.

All types of pain present in this disease are amenable to treatment with the exception of that attributable to severe degrees of ischemic neuritis.

The decrease in the incidence of amputation in cases of thromboangiitis obliterans has followed, to a large degree, the effective treatment of pain.

Brams, William A., Golden, J. S.: The Early Response of Venesection With Observations on So-Called Bloodless Venesection. Am. J. M. Sc. **189:** 813, 1935.

So-called "bloodless venesection" failed to reduce venous pressure or to modify pulse rate or arterial pressure in patients with cardiac failure. These results are in contrast to the changes observed in the same patients after bloodletting.

The effects of ordinary venesection were studied in fifteen patients with cardiac failure. Observations were made every five minutes for a period of one hour after venesection was completed.

It was exceptional for either the systolic or diastolic arterial pressure to show an appreciable fall after venesection or during the period of observation. The same results were observed in patients with arterial hypertension as in those with normal pressure.

The pulse rate remained unchanged in all experiments.

Venous pressure fell consistently after bloodletting, the maximum drop occurring immediately after completion of venesection. The fall began early in the course of venesection, becoming apparent after removal of the first 100 c.c. of blood and continuing to drop as more blood was withdrawn. A partial return toward the control level within a few minutes was observed in the majority of instances, but the level of venous pressure after an hour was usually lower than the control level.

The fall in venous pressure was especially marked in cases in which venous hypertension existed, and the actual drop also depended greatly on the quantity of blood removed. The greatest drop usually occurred in cases of venous hypertension in which from 600 to 800 c.c. of blood were removed, though it so happened that a level nearer to normal was reached in the cases with a smaller blood removal.

The practical significance of the fall in venous pressure after venesection, in relation to cardiac failure, is briefly discussed.

Morlock, Carl G., Horton, Bayard T.: Variations in Blood Pressure in Renal Tuberculosis. Am. J. M. Sc. **189:** 803, 1935.

As a result of the analysis of the systolic blood pressures of 346 patients who had proved renal tuberculosis, we cannot concur in the opinion generally expressed that an active tuberculous lesion, regardless of its situation, has an accompanying arterial tension lower than normal. In the series of cases analyzed it was found that the vast majority of patients (approximately 76 per cent) had normal blood pressures, 22 per cent had hypertension—that is, a systolic pressure of 140 mm. of mercury or more—and approximately 2 per cent had hypotension—that is, a systolic blood pressure less than 100 mm. of mercury. The number of patients in this series with hypertension or hypotension was not any greater than was found in a larger control series of normal individuals in the same age groups.

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Original Communications

THE PRODUCTION OF A COLLATERAL CIRCULATION TO THE HEART

I. An Experimental Study*†‡

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It is a perversity of nature that the most important muscular structure in the body is the most defenseless. If the blood supply to an extremity is cut off by an obstruction to a major artery, a collateral circulation to the extremity usually develops, and function is restored. If the blood supply to the heart is cut off by an obstruction to a major artery, the heart may come to a complete and permanent standstill, and little or no opportunity is afforded for a collateral circulation to develop. The appalling incidence of sudden death from heart failure in our adult population attests to the destructive nature of coronary disease.

Man's anatomical pattern provides the heart with two almost frictionless surfaces which constantly glide over each other. The only direct continuity of the heart with the rest of the body is through the walls of the great vessels, the fat, the nerves, and the lymphatics which form an anchorage for the heart, so to speak, at its base. While the heart is in direct contact with other structures over its entire surface, it has a minimum amount of direct continuity with such adjacent structures. Unwittingly, nature to a marked degree has deprived the heart of a most important compensatory property, namely, that of developing an adequate collateral blood supply to meet an emergency, to preserve life during the first moments, hours, days, and weeks after a serious coronary

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accident. If life is preserved over a sufficiently long period of time, the process of coronary occlusion can go on to completion.[1] In other words, complete closure of the coronary ostia at the aorta is compatible with life. In these cases the myocardium draws from other sources for its blood supply. The substitution of another source of blood supply for the normal source of blood supply must be done slowly. It can be done, but the number of times that nature has succeeded in making this substitution is excessively small. At some place along the way life is snuffed out like a candle flame.

Under normal conditions the heart has three sources from which it can receive a supply of blood: the coronary arteries, the thebesian vessels, and the extracardiac anastomoses between the coronary system and the blood vessels in the fat and other tissues at the base of the heart. The tissues at the base of the heart normally are not richly vascularized, but communications between the coronary system and the vessels in these tissues have been demonstrated.[2] Blood vessels have been demonstrated also in adhesions between heart and pericardium.[3] These extracardiac anastomoses were demonstrated by the injection of lampblack into the coronary system. That such blood vessels exist in adhesions to the human heart was confirmed by direct observation at operation (C. S. Beck, Nov. 10, 1934). In this instance an adhesion extended from the base of the left ventricle to the parietal pericardium. When the adhesion was cut, active bleeding occurred from each end of the transected tissue. The bleeding appeared to be more brisk from the cardiac end than from the pericardial end. This is the first direct observation of the functional nature of such blood vessels in man.*

Our interest in the production of a collateral vascular bed to the heart was an outgrowth of a discussion that Dr. Alan R. Moritz had with the senior author of this paper (C. S. Beck) toward the close of 1931. He directed attention to the presence of blood vessels in pericardial adhesions in cases without any coronary occlusion and also in cases with coronary occlusion. He referred to the case reported by Thorel[4] in 1903—in a patient who had pericardial adhesions and complete obliteration of both major coronary arteries. It was suggested by Thorel and emphasized by Moritz that these adhesions provided a blood supply to the heart. On the basis of this information it became our intention to produce experimentally a new vascular bed to the heart. The first experiments with this purpose in mind were done by Beck in February, 1932. Dr. Moritz followed the work with interest and gave us valuable suggestions concerning the injection and study of the specimens.†

*We observed the vascular nature of cardiopericardial adhesions in experimental animals several years ago in our studies of chronic cardiac compression.

† We also desire to thank Dr. Carl Wiggers, Dr. Carl Lenhart, Dr. Howard T. Karsner, and Dr. Joseph T. Wearn for suggestions and interest in the work, and also the various internes in the Lakeside Hospital for assistance in many of the operations.

METHOD

The problem of producing a new blood supply to the heart resolved itself into two components. One was to make available a satisfactory vascular bed for the heart. The other was to produce the stimulus which would bring about continuity between the cardiac and extracardiac vascular beds. The work progressed largely by virtue of the trial and error method. The operative procedure underwent almost constant evolution.

The available bed for vascularization of the myocardium consists of the pericardium, pericardial fat, mediastinal tissues, pleura, diaphragm, substernal muscles, the musculature of the thoracic wall, and the omentum. In these experiments the pericardium, the pericardial fat, and the mediastinal tissues were utilized for the vascular bed (Figs. 1 and 2). A series of experiments is now being carried out in which adjacent muscles are being utilized for the source of blood supply. We are also carrying out experiments in which the omentum is brought to the heart through an opening in the diaphragm. Direct continuity between the vascular bed and the heart was established by the production of adhesions. The methods of producing adhesions were by incision of myocardium and suture of pericardium into the wound or by removal of epicardium and endothelial lining of the pericardium. Sandpaper, emery paper and finally special burrs were used for this purpose. The stimulus necessary to bring about vascular continuity between the extracardiac and cardiac beds was a reduced or subnormal pressure in the coronary bed.* The pressure was reduced by occluding the coronary arteries. The flow through the coronary arteries can be reduced either slowly by successive operations or by complete ligation in one stage. The obstruction can be applied to major coronary trunks or anywhere toward the peripheral branches. Obviously the most desirable form of coronary obstruction is a slowly progressive obstruction going on to complete obstruction. With this purpose in mind, bands of periosteum were wound around the coronary arteries at their origins from the aorta. The most satisfactory method of producing gradual occlusion of a major coronary artery was that of repeated operation. We used clips that we made from sheet silver. These clips were shaped as illustrated (Fig. 3) and were progressively clamped together at successive stages. In order to locate the clip at operation a piece of silk or wire was looped around the artery close to the clip, and the ends were left long so that they could be found later at operation. If at a subsequent operation the clip could not be dissected free of scar tissue, complete occlusion of the artery was effected by means of the silk or wire loop.

*Perhaps the variation in mediastinal pressures accompanying respiration can augment the development of collateral vessels to the heart. The alternate application of positive and negative pressure to an extremity can augment the blood supply to the extremity. Perhaps active exercise of the animal would have been valuable in these experiments.

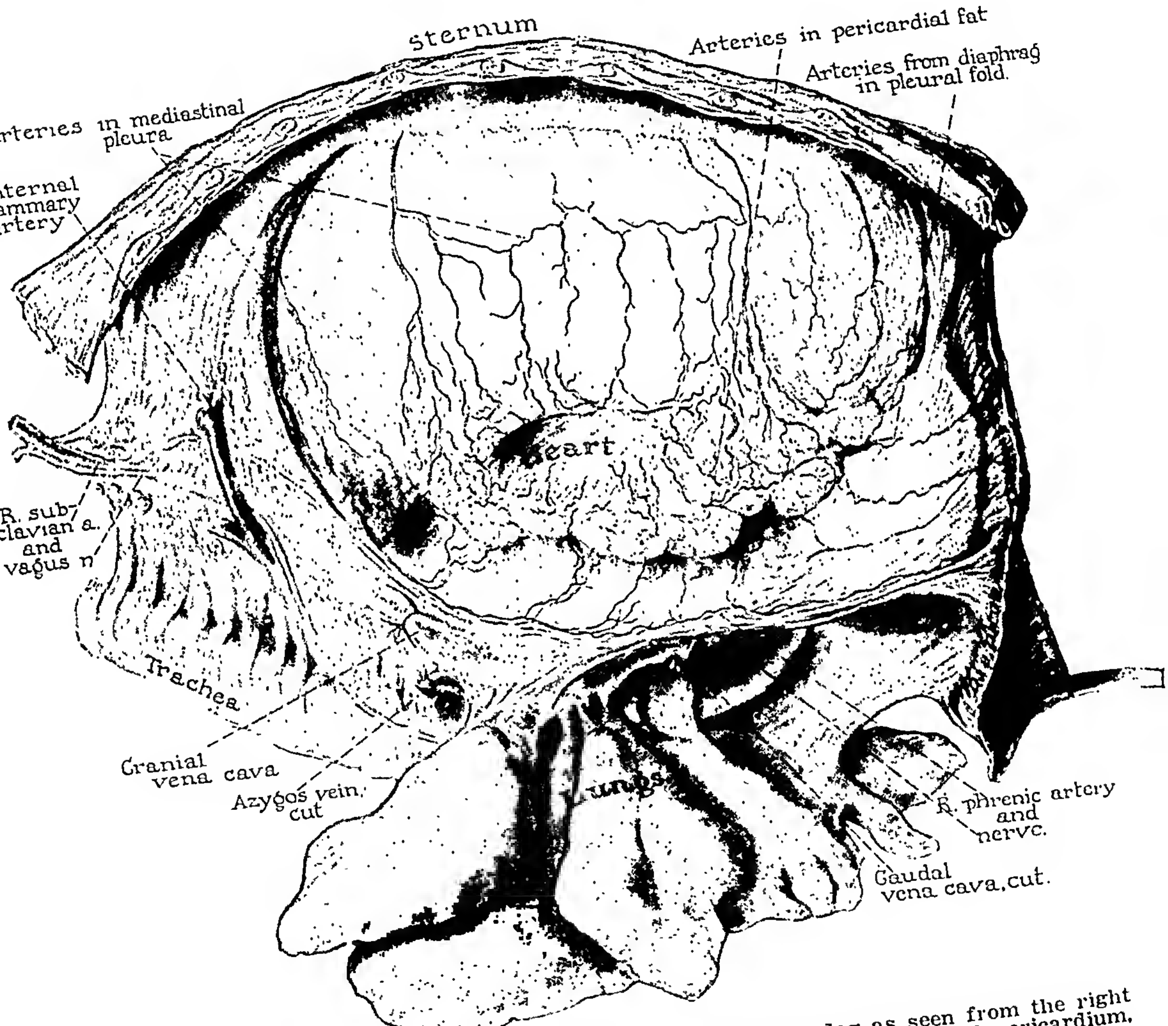

Fig. 1.—The available vascular bed to the heart in the dog as seen from the right side of the chest. This bed consists of the pericardial fat, the parietal pericardium, and the mediastinal tissues. The internal mammary arteries and the substernal muscles can also be transplanted to the surface of the heart.

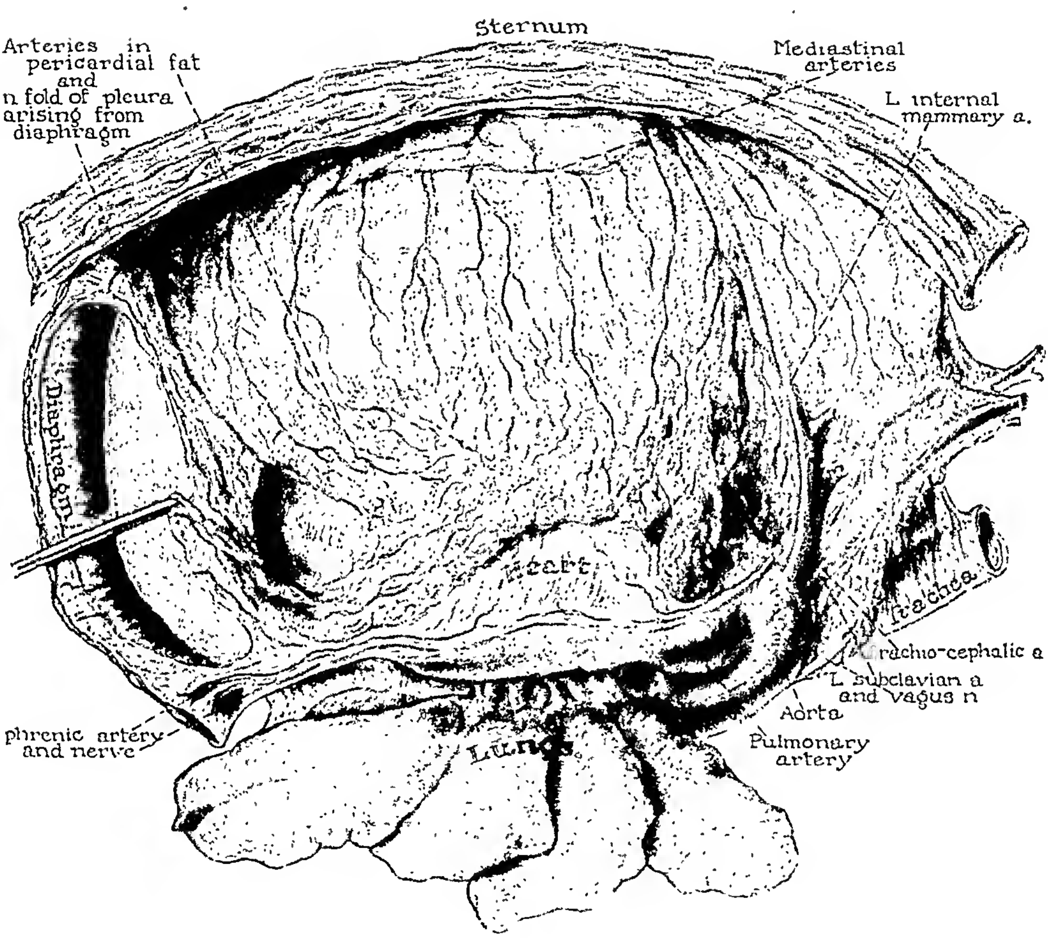

Fig. 2.—The available vascular bed in the dog as viewed from the left side of the chest.

The anastomoses between the extracardiac vascular bed and the heart were determined by the injection of ferric ferrocyanide. The dye was injected into the collateral bed from the aorta, the ostia of the coronary arteries and the thebesian channels being excluded from the injection system (Fig. 4). The usual order of procedure was as follows:

The dog was anesthetized with ether through an intratracheal tube. Mechanical respiration was used. The right carotid artery was connected to a flask. The left carotid artery was connected to a mercury manometer. The inferior vena cava was isolated at its junction with the auricle. A T-tube was placed in this vessel; the long arm of the tube was clamped, and blood was allowed to run through the short arm into the auricle. The superior vena cava and the azygos vein were isolated (but not ligated) close to the auricle. The clamp was removed from the long

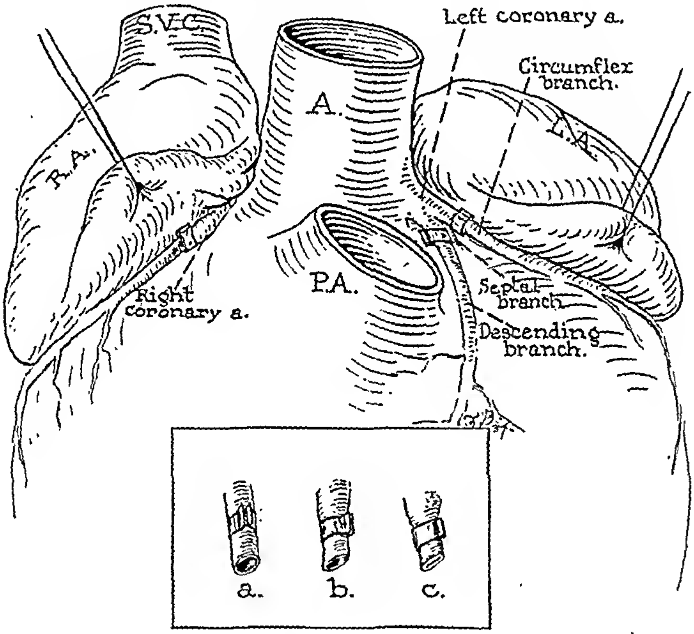

Fig. 3.—The usual site of producing occlusion of the coronary arteries by bands or clips made from sheet silver. The clips are compressed in successive stages as indicated in *a*, *b*, and *c* of the inset.

arm of the T-tube in the inferior vena cava, and the animal was bled. Two liters of normal saline at a temperature of 38° C. was washed through the circulation by way of the flask connected to the right carotid artery. The superior vena cava and the azygos vein were then ligated close to the auricle. The inferior vena cava was clamped between auricle and cannula. The right auricle was incised so that we were certain that fluid could not enter the heart. The aorta was securely clamped close to its origin, and the aorta was cut across between clamp and heart so that fluid could not enter the ostia of the coronary arteries. Following this, 0.4 per cent of aqueous solution of ferric ferrocyanide at normal body temperature was injected under gravity pressure of about 180 cm. The injection was continued for 30 minutes. The pressure

in the left carotid artery usually varied from 100 to 120 mm. Hg during the injection. The dye was allowed to escape from the inferior vena cava during the injection. Usually about eight liters of the dye were used. Usually the heart continued to beat up to, and even for a few moments after, the injection of dye was started. With the heart segre-

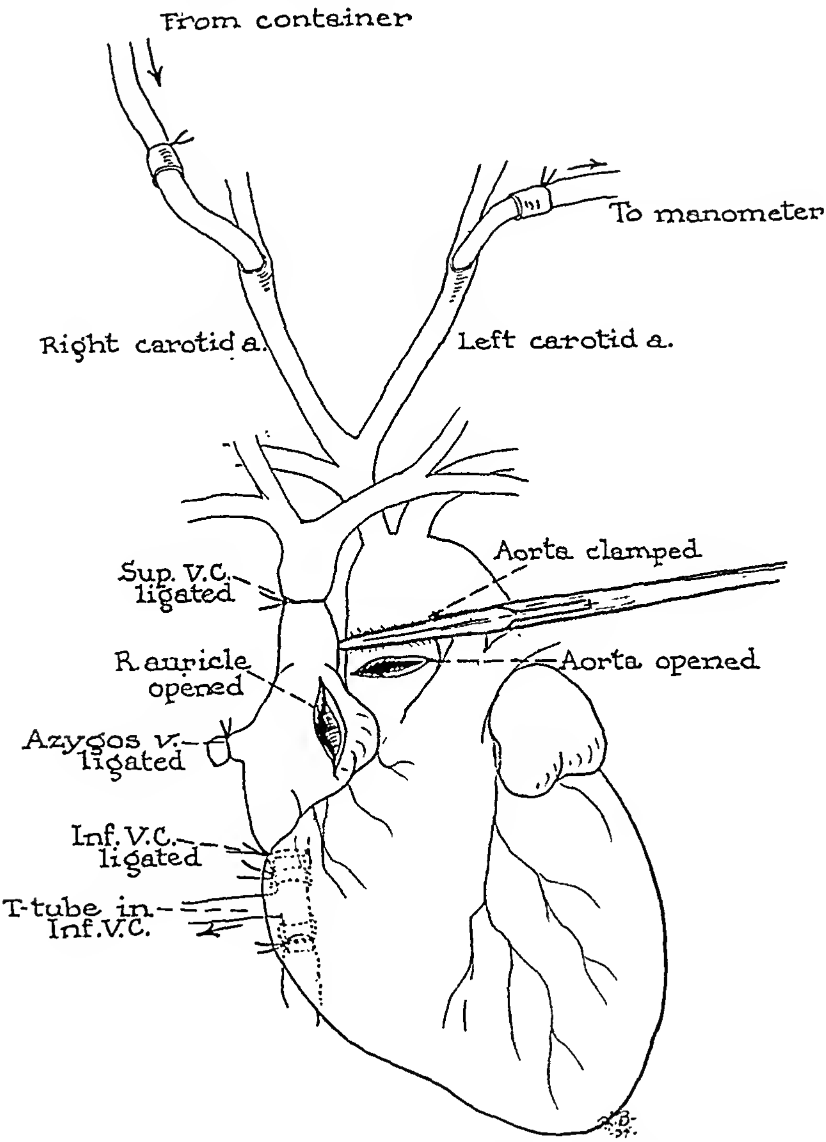

Fig. 4.—Method of injection of heart through extracardiac anastomoses. The ostia of the coronary arteries and of the thebesian channels are isolated from the injection system. Dye can enter these structures only through anastomoses with the extracardiac vessels.

gated from the circulation (except for the extracardiac collateral vascular bed) and with the right auricle and aorta opened, it was considered to be impossible for any of the dye to enter the myocardium through the ostia of the coronary arteries or through the thebesian vessels. The heart was not touched or massaged in any way while the injection was in

progress. Under these conditions the myocardium could be injected only through the extracardiac anastomoses. An alternative method of injection, which we rarely used, consisted of cannulating the coronary arteries and injecting the coronary system and then determining the spread of the injection into the extracardiac tissues.

A number of attempts were made to carry out the injection and at the same time have the heart receive and expel its usual quota of blood. These experiments were not successful and will not be recorded.

EXPERIMENTS

This report is based upon the study of 103 dogs in which one or more operations were carried out to produce a collateral circulation to the heart, and upon sixteen dogs in which various methods were used for injection of the heart through the extracardiac anastomoses. One hundred and sixty-five operations were performed on the 103 dogs. On some of the dogs as many as four operations were performed. Many of the operations consumed three or four hours, and some of them were something of an achievement in technical surgery.

The following protocols are given as illustrations of the various types of experiment that were done.

Protocol 1.—Dog No. 33-131. This was a normal dog. Injection of the extracardiac anastomoses was carried out. The mediastinal tissues, pericardial fat, and parietal pericardium were diffusely stained. The right and left coronary arteries were filled with dye. A trace of dye was seen in each auricle near the entrance of the great veins. On cross-section of the heart the only dye seen was in the main trunks of the coronary arteries (Fig. 5). There was no dye in the myocardium either grossly or microscopically.

Protocol 2.—Dog No. 33-146. This was a normal dog. Injection of the extracardiac anastomoses was carried out. The mediastinal tissues, pericardial fat, and parietal pericardium were diffusely stained. The right and left coronary arteries together with their superficial branches contained dye. The fat at the base of the aorta was stained and the auricles were faintly blue; the left auricle was stained a little more than the right. Cross-section showed dye in the larger branches of the coronary arteries to a greater extent than in the preceding specimen (Fig. 6). Microscopically the left auricular appendage contained arteries filled with dye, but there was no capillary injection. Extensive but focal capillary injection was present in a section of the right ventricle limited to the narrow zone of myocardium that extends out for a short distance in the wall of the pulmonary vein. Several fairly large arteries (one measured 150 micra in outside diameter) extended between the heart and the extracardiac structures.

Protocol 3.—Dog No. 33-141. This was a normal dog. Injection of the extracardiac anastomoses was carried out. The pericardial fat and the parietal pericardium were well injected. Dye contained in vessels could be seen entering the auricles and the conus arteriosus with some extension into the ventricular myocardium at the base of the heart. The largest anastomotic vessels were the vasa vasorum of the pulmonary artery and of the aorta. The adventitial fat around the great vessels was well injected. The surface of the heart showed some diffuse injection which was most marked just below the atrioventricular sulcus. The superficial

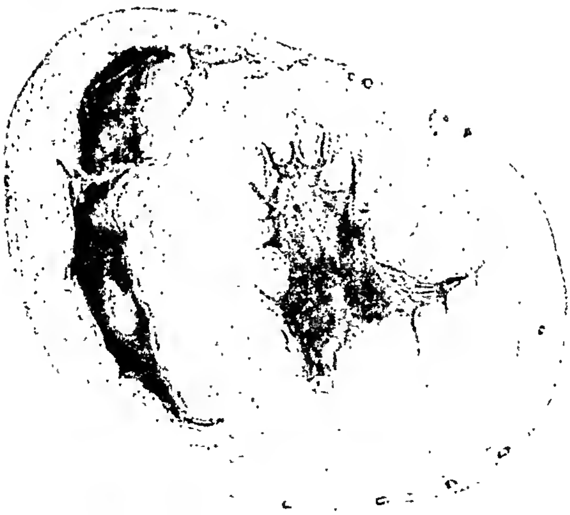

Fig. 5.—Protocol 1 (Dog No. 33-131). Normal heart after injection with dye.

branches of the coronary arteries were filled with dye. On cross-section some dye was present in the superficial portion of the myocardium, especially in the left ventricle. The walls of both auricles were fairly diffusely injected. There was no diffuse staining of the myocardium grossly (Fig. 7). Microscopically all the large and most of the small arteries in a section of the left auricular appendage contained dye. This section also showed focal, scanty capillary injection. A section of the left ventricle showed that all the large vessels and many of the small vessels contained dye. This section also showed some focal, scanty capillary injection. The section showed questionable fibrosis. There was no infarction. A section of the right ventricle showed that some of the large and very few of the small arteries contained dye. The epicardium and the subepicardial portion of the myocardium showed slight focal capillary injection.

These specimens represent the slightest and the greatest degree of injection through the extracardiac anastomoses that we found in our series of normal dogs.

Protocol 4.—Dog No. 34-18. Feb. 27, 1934: A loop of wire and a silver clip were placed around the two major branches of the left coronary artery below its bifurcation. The circumflex branch was constricted about four-tenths. The right coronary artery was constricted about one-half of its normal cross-section. Throughout this operation great beads of clear fluid were observed to form on the surface of the heart.* Epicardiectomy† was done with our special burrs, and the endothelial lining of parietal pericardium was roughened with these burrs. Death occurred March 3, 1934, from cardiac failure. The degree of occlusion of the coronary arteries was too great.

Protocol 5.—Dog No. 33-30. April 18, 1933: A loop of silk and a loop of periosteum were placed around each major branch of the left coronary artery just below its bifurcation and also around the right coronary artery close to its origin from the aorta. These vessels were not constricted by these loops of silk and periosteum. The strand of periosteum was taken from a rib and was about 3 mm. in diameter. The epicardium and the inner surface of the parietal pericardium were scraped with a scalpel. The pericardium was sutured to the heart. Dec. 10, 1934: The animal was killed, and the heart was injected. Generalized adhesions to the pericardium and pericardial fat were present. These tissues were deeply injected. When the myocardium was cut across, it was found that the dye had not penetrated the myocardium. The coronary arteries showed no constriction. Our interpretation of this experiment was that in the absence of partial occlusion of the coronary arteries vascularization of the myocardium from the adherent pericardium did not take place. In other words, there was no unusual need for additional blood during life, and no additional vascularization of the myocardium took place (see Protocol 15).

Protocol 6.—Dog No. 33-62, weight 13.6 kg. June 14, 1933: The left coronary artery was isolated at its bifurcation. A loop of silver wire was placed around the descending and the circumflex arteries. A silver clip was placed around the circumflex branch occluding its lumen to a moderate degree. A silver clip was placed on the

*This is the second observation of drops of fluid forming from the heart in an experience of over a thousand experimental operations on the heart (C. S. B.). Fluid formed at one point like a bead of perspiration every few seconds.

†In so far as we know this is the first time that the term epicardiectomy has been used and in so far as we know this is the first time this operation has been done. In some animals the epicardium came away in large sheets; in others it came away in shreds. The epicardium is quite tough and undoubtedly gives considerable support to the myocardium. It is of considerable importance as a surgical structure. It helps to prevent sutures from tearing out of the heart and in this respect is not unlike the submucosa of the small intestine.

Fig. 6.—Protocol 2 (Dog No. 33-146). Normal heart after injection with dye.

descending branch occluding its lumen to a somewhat greater degree. A loop of wire and a silver clip were placed around the right coronary artery where the vessel lies beneath the right auricle. This vessel was occluded partially. The epicardium was roughened with a burr and in certain areas was entirely removed. The parietal pericardium was roughened and torn with the burr. The animal made an excellent recovery. Oct. 2, 1933: Reoperation—The silver wires were brittle and were easily broken. The clip on the right coronary artery was located. It was crushed and the right coronary artery was completely occluded. The silver wires on the branches of the left coronary artery were isolated. The wire on the circumflex branch was tightened producing total occlusion. Since the heart could not stand total occlusion of the circumflex artery, the tension on the artery was released. Tension applied to the wire on the descending artery was tolerated, and the wire was twisted tightly to occlude this vessel completely. Oct. 6, 1933: The animal appeared to be in excellent condition. He was active and playful. The electrocardiogram showed high take-off of the T-wave in Leads I and II. Sept. 28, 1934: (Weight 14.5 kg.) The dog was killed for study of the specimen. The injection was carried out as already outlined. Grossly the adherent fat and pericardium, as well as the entire muscle, were diffusely injected (Fig. 8). There was a small cicatrix (about 12 mm. in diameter) in the lateral wall of the right ventricle which was judged to represent a healed infarct. Microscopically there was extensive capillary injection in sections taken from six different portions of the heart. Examination of the left coronary artery showed the descending branch to be completely occluded, the circumflex branch to be patent only to a fine probe, measuring about 2 mm. in circumference, and the septal branch to be intact. The septal branch measured 3.5 mm. in circumference. The right coronary artery was completely occluded about 1 cm. from the aorta. There were six very fine twigs that could be identified coming off the right coronary artery between the clip and its ostium in the aorta. We estimated that the total cross-sectional area of the coronary arterial system was reduced about 85 per cent.

Protocol 7.—Dog. No. 32-51, weight 18.5 kg. Mar. 23, 1932: The pericardium was sutured to the left side of the thoracic wall for a purpose other than for these experiments. Mar. 21, 1933: The attachment to the thoracic wall was incised, and the heart was exposed. Superficial incisions were made over the surface of the ventricles with a scalpel. The pericardium was sutured to the heart and also to the thoracic wall. Sept. 1, 1933: A silver clip and a wire loop were placed around each major branch of the left coronary artery just below its bifurcation. The heart stopped. The wire was removed, but clips were left in place. Epinephrine and massage were used, and the heart started to beat. Some obstruction was given to each major branch of the left coronary artery. The heart action was irregular. The right coronary artery was not isolated. Feb. 17, 1934: An attempt was made to isolate the right coronary artery. Several mass ligatures were placed in what was considered the anatomical location of the right coronary artery. Scar tissue obscured its location. Oct. 2, 1934: The animal was in good health. It was active and well nourished and weighed 17.0 kg. Two and one-half years had elapsed since the first operation. The animal was killed for study. The heart was injected, and the specimen was cut and examined by Dr. Moritz, Dr. Wiggers, Dr. Lenhart, and Dr. Karsner. The measurements as given by Dr. Moritz were as follows: The right coronary artery for a distance of 3 cm. from its ostium had a circumference of 4 mm. There was no obstruction to this vessel. The left coronary artery just below its ostium and above its bifurcation had a circumference of 9 mm. The ramus descendens had a circumference of 3 mm. at the site of obstruction and 6 mm. below the silver clip. The artery above the clip was narrowed. The septal branch came off above the obstruction. It was a very small vessel. The circumflex artery was

Fig. 7.—Protocol 3 (Dog No. 33-141). Normal heart after injection with dye. This specimen shows the greatest amount of injection through the extracardiac anastomoses found in our series of sixteen normal specimens.

reduced to a circumference of 1.5 mm. at the site of the obstruction. Below the clip it measured 6.5 mm. in circumference. According to these measurements the cross-section of the ramus descendens was reduced about 75 per cent and the cross-section of the ramus circumflexus was reduced about 95 per cent. The right coronary artery was relatively a small artery, and it appeared that an extracoronary collateral circulation was established in preference to compensation by enlargement of the right coronary artery. There was complete fibrous obliteration of the pericardial cavity. There was diffuse injection of the myocardium although there was some variation in intensity of the dye. The least injected portion was the anterior papillary muscle in the left ventricle. Although there was no infarction, there was considerable focal myocardial fibrosis. This scarring was most extensive in the posterior portion of the interventricular septum and left ventricle. Microscopically the capillary injection was extensive (Fig. 9), and sections taken from six different portions of both ventricles failed to disclose differences in distribution of dye described grossly. The amount of Prussian blue in skeletal muscle was 89 mg. per 100 gm. of muscle and the amount of dye in the cardiac muscle was 84.5 mg. per 100 gm. of heart.

Protocol 8.—Dog No. 33-139. Dec. 12, 1933: The left coronary artery was isolated at its bifurcation, and a loop of wire and a silver clip were placed around each major trunk. Some obstruction was given to each artery. The right coronary artery was isolated, and its lumen reduced about one-half. The epicardium and parietal pericardium were roughened with a burr. June 28, 1934: An attempt was made to reduce further the lumen of one branch of the left coronary artery. The clips and wire loops were covered with scar tissue, and accurate isolation was impossible. Oct. 2, 1934: The animal was killed, and the specimen was injected (Fig. 10). The cross-sectional area of the right coronary artery was reduced about 25 per cent. The left coronary artery showed slight reduction in lumen by the clips. The cardiac muscle contained 22 mg. of Prussian blue per 100 gm. of muscle, and the skeletal muscle contained 107 mg. of dye per 100 gm. of muscle. The pericardial cavity was obliterated, but parietal pericardium could be stripped from the heart. The adhesions were not very dense. There was some diffuse injection of both auricles. There was slight injection of the ventricles, more marked in the right than in the left. There was no sign of myocardial fibrosis or infarction. Microscopical sections showed some diffuse injection of large and small arteries of both ventricles, more marked in the right than in the left. There was very little capillary injection in the inner half of the left ventricle. The adhesions to the myocardium were richly vascularized by small vessels containing dye. There was no fibrosis or infarction in the sections.

Protocol 9.—Dog No. 34-4. Jan. 15, 1934: The left coronary artery was isolated and a wire loop and a silver clip were placed around each major branch. The reduction in lumen was estimated to be one-half. Similarly the right coronary artery was constricted about one-half by a silver clip. July 11, 1934: The clip on the descending branch of the left coronary artery was isolated and the lumen was further reduced. Oct. 3, 1934: The animal was killed, and the heart was injected. There was apparently complete injection of the parietal pericardium. The pericardial cavity was obliterated by fibrous adhesions. Both ventricles showed diffuse but incomplete injection with dye. The degree of injection was greater in the anterior portion of the left ventricle extending from base to apex. This area was supplied by the ramus descendens of the left coronary artery. There was no gross or microscopical evidence of fibrosis or infarction. Microscopically many large dye-containing vessels were present in the myocardial adhesions. The sections of myocardium taken for examination showed diffuse capillary injection with dye. The ramus descendens was obstructed more than the ramus circumflexus. The circumference of the ramus descendens at the clip was 5 mm., below the clip 7 mm. The

Fig. 8.—Protocol 6 (Dog No. 33-62). Extensive injection of the myocardium through the vascular bed established by operation. New blood vessels can be seen.

Fig. 10.—Protocol 8 (Dog No. 33-139). A slight degree of injection with dye in response to a slight degree of coronary obstruction.

injection. The interventricular septum showed a scanty injection, and the wall of the left ventricle showed a superficial injection (3-5 mm.). There was no apparent fibrosis or infarction. Capillary injection of the right ventricle was present in the more superficial portion. The large and small arteries of the right ventricle were everywhere injected. The left ventricle showed less injection than the right. One small infarct was found. The ramus descendens was completely occluded just below the bifurcation of the left coronary artery. The ramus circumflexus showed no occlusion.

Protocol 11.—Dog No. 33-16. Mar. 30, 1933: The left coronary artery was isolated at its bifurcation and a loop of periosteum was placed around each of the two major branches. The degree of constriction on the ramus descendens had to be reduced because the heart stopped. It was revived, and the loop of periosteum was again applied. The epicardium and parietal pericardium were scraped with a scalpel. Sutures were placed between pericardium and myocardium. June 1, 1933: The ramus circumflexus could not be isolated. The ramus descendens was ligated completely at its origin. An attempt to isolate the right coronary artery was not successful. Mass sutures were placed in an attempt to ligate this artery. The animal had sharp pain after operation, most probably coronary pain. Morphine was given. Mar. 13, 1934: The animal was killed and the heart was injected. The pericardium was adherent to the auricles, to the base, anterior and lateral aspects of the heart. An extensive injection of the left ventricular wall was present (Fig. 11). Slight injection of the right ventricular wall was found. The auricular walls showed slight injection. There was no gross or microscopical evidence of fibrosis or infarction. Sections including the fused pericardial surfaces showed rich vascularization of the intervening connective tissue. These vessels were uniformly filled with dye. The arteries and capillaries of the right and left ventricles and interventricular septum contained dye. The capillary injection varied in extent and was most pronounced in the superficial portion. Nowhere was complete capillary injection found. Focal fibrosis, but no infarction, was found in each ventricle. These areas of fibrosis were probably due to the sutures that were placed in the myocardium. The ramus descendens was completely obstructed. The ramus circumflexus was slightly constricted but was easily patent to a probe. The right coronary artery was slightly constricted but also admitted a probe readily.

Protocol 12.—Dog No. 33-42. May 17, 1933: The left coronary artery was isolated. A loop of silk and a silver clip were placed around the circumflex branch. The ramus descendens was unusual in that there were three separate descending arteries instead of one. A large vein crossed these arteries. The clip on the circumflex artery reduced the lumen about one-half. The epicardium and the inner surface of the pericardium were roughened with emery paper. Aug. 7, 1933: Two relatively large vessels were seen extending from the pericardial fat to the region of the internal mammary vessels. The pericardial tissues were more vascular than normal. The braided silk loop around the circumflex artery was isolated, and this artery was ligated. A silver clip and a loop of silk were placed on the right coronary artery. This artery was partially occluded. Oct. 10, 1933: The braided silk around the right coronary artery was isolated, and a knot was tied in the silk. The clip could not be found. There was good recovery. Feb. 22, 1934: The animal was killed for study; the specimen was injected. The parietal pericardium was diffusely injected. The pericardial cavity was completely obliterated. A multilocular organized abscess was found at the base of the heart to the left of the pulmonary conus. The adhesions showed a diffuse injection with dye. The superficial branches of the coronary arteries were completely filled with dye. The myocardium was diffusely injected. The right ventricle showed a deeper injection than the left ventricle.

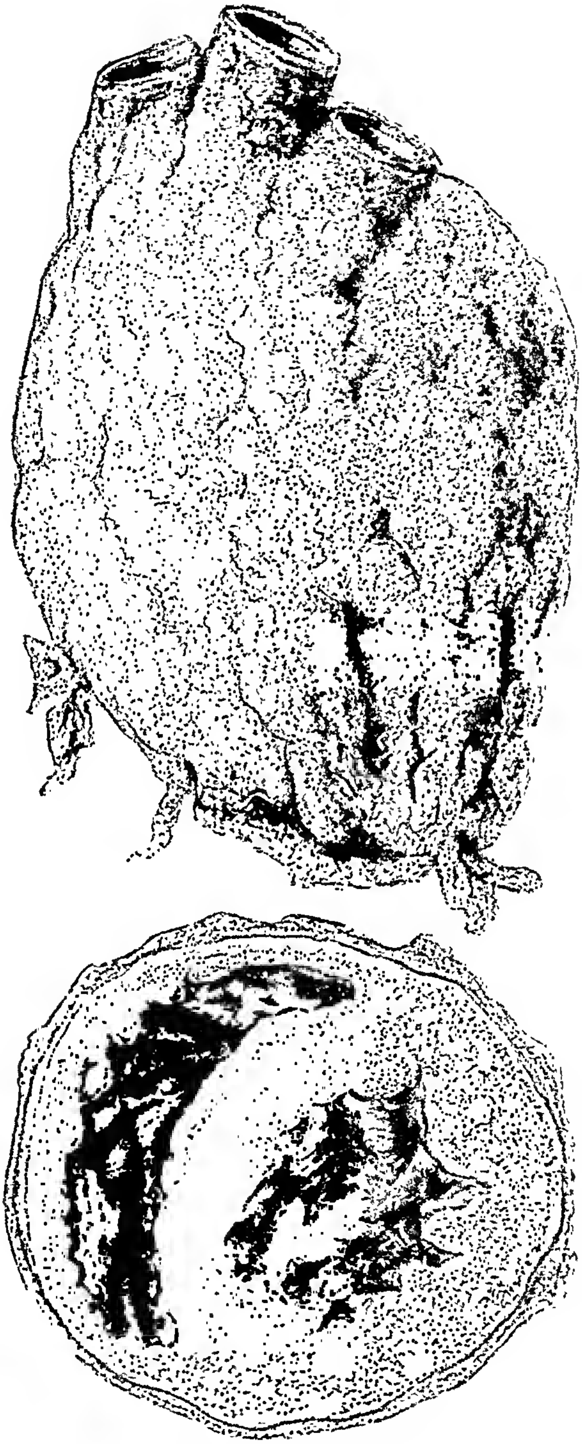

Fig. 11.—Protocol 11 (Dog No. 33-16). The collateral vascular bed was well injected. There is some injection of the myocardium, particularly the left ventricle.

The least injected portion of the heart was a zone adjacent to the endocardium of the left ventricle. Microscopical sections showed extensive injection of arteries and capillaries in the pericardial adhesions, in the entire thickness of the right ventricle and in the external two-thirds of the left ventricle. There was no fibrosis or infarction. The circumflex branch of the left coronary artery was completely occluded and the right coronary artery showed almost complete occlusion admitting only a very fine probe. The descending branches of the left coronary artery were intact.

Protocol 13.—Dog No. 33-144. Dec. 12, 1933: A wire loop and a silver clip were placed around the right coronary artery and the two major branches of the left coronary artery. A silver clip was placed around the septal branch, which in this dog was larger than usual. The lumen of each of these vessels was reduced about one-half. The burr was used on the epicardium and pericardium. The animal developed a pulmonary infection and died Jan. 11, 1934. Patchy areas of consolidation were present in the lung. The animal was injected. The pericardial cavity was obliterated. This obliteration was fibrous over the apex of the heart and the lateral surface of the left ventricle; elsewhere it was fibrinous. There seemed to be complete injection of the parietal pericardium and filling of the superficial branches of the coronary arteries, with extensive focal myocardial injection of both ventricles. The injection of the myocardium exceeded that seen in any of the normal hearts. Each of the major coronary arteries was partially constricted. The clip on the circumflex branch at its origin reduced the lumen at least one-half. The ramus descendens was markedly occluded, and it is questionable whether the obstruction had not been complete. The right coronary artery was markedly constricted. It was not patent to the smallest probe although the lumen contained dye. Microscopically the large and small superficial arteries contained dye. The capillary injection of both ventricles was focal, but in some sites it was extensive. It was significant that evidence of a collateral circulation appeared in three weeks from the original operation.

Protocol 14.—Dog No. 34-9. Jan. 25, 1934: Each branch of the left coronary artery was surrounded by a silver clip and a loop of wire. The lumen of each artery was reduced approximately one-half. The right coronary artery was partially occluded. July 11, 1934: The ramus descendens was completely occluded. Ventricular fibrillation occurred, and the heart stopped. Study of the specimen showed fibrous obliteration of the pericardial cavity except over the anterolateral upper portion of the left ventricle. A good injection of the parietal pericardium was obtained. Incomplete filling of even the superficial branches of the coronary arteries was found, and there was very little myocardial injection. The myocardial injection was no more than one finds in normal hearts. The right coronary artery was markedly reduced; the lumen was about 1 mm. in diameter. The ramus descendens of the left coronary artery was similarly reduced. Despite what was considered significant reduction in the lumina of the right coronary artery and the ramus descendens of the left, together with extensive pericardial adhesions, no significant anastomosis could be demonstrated through the adhesions. This failure in the development of collateral anastomosis was the only one obtained in these experiments. Microscopically the larger arteries contained dye. In superficial focal areas some capillary injection was found. The deeper portion of the myocardium was not injected. There was no evidence of fibrosis or infarction.

Protocol 15.—Dog No. 33-28. Apr. 15, 1933: A loop of periosteum was placed around the left coronary artery above its bifurcation. Hemorrhage from the aorta was encountered but was controlled. The endothelial surface of the parietal pericardium was scraped with a scalpel. The pericardium was sutured to the myo-

cardium. June 8, 1933: A mass suture was placed for the purpose of occluding the ramus circumflexus. Dec. 19, 1933: The right coronary artery could not be isolated. A mass suture was taken for the purpose of occluding it. Likewise a mass suture was placed for the purpose of occluding the ramus descendens of the left coronary artery. Feb. 6, 1934: Another attempt was made to occlude the ramus descendens of the left coronary artery by placing a mass suture. Oct. 1, 1934: The dog had been active but had lost weight. It was killed for study. The right coronary artery was normally patent. The ramus circumflexus of the left coronary artery was normally patent throughout its course. The ramus descendens was occluded by not more than one-third its cross-section. There was complete injection of the parietal pericardium and complete obliteration of the pericardial sac by dense fibrous adhesions. The superficial branches of the coronary arteries were filled with dye. There was very scanty incomplete injection of the myocardium, more marked in the right ventricle than elsewhere. Microscopically all arteries contained dye as did also many arterioles. Capillary injection of the epicardium was present. The capillary injection of the myocardium was scanty. The epicardium was greatly thickened and fused with parietal pericardium. The adhesions were richly vascularized. No myocardial fibrosis or infarction was found. This experiment would indicate that there was little or no need for the production of a collateral circulation.

DISCUSSION OF EXPERIMENTS

These protocols, recorded briefly as they are, indicate in a general way the results that were obtained in a considerably larger series of experiments and operations. The fatal nature of many of the experiments, the difficulty in the technical performance of the operations, the variety of the operative procedures that were evolved as the work progressed made it necessary to carry out a larger number of experiments than otherwise would have been necessary.

When we began these experiments, we desired to destroy or to obstruct the entire arterial coronary circulation and have a new collateral circulation develop to take its place. We did not succeed in doing this, but we almost succeeded. In one of the experiments about 85 per cent of the total cross-sectional area of both coronary arteries was occluded (right coronary artery completely occluded, ramus descendens completely occluded, ramus circumflexus markedly constricted), and this animal survived and was normally active. In several experiments complete occlusion of the ramus descendens was effected with recovery of the animal. Complete occlusion of the ramus circumflexus was effected with recovery of the animal. Complete occlusion of the right coronary artery was effected with recovery of the animal. In other experiments partial occlusion of both right and left coronary arteries was effected with recovery of the animal. This is the first time such extensive occlusions of the major coronary arteries have been effected experimentally. Disease can accomplish this in man provided the occlusions are gradual so that a compensatory circulation can develop.

In a series of experiments which is now in progress, total occlusion of the right coronary artery in one stage was tolerated, but in these experiments a collateral vascular bed had been prepared for the heart

at a previous operation. We believe this observation is of considerable significance because in our experience total occlusion of the right coronary artery in one stage has carried a high mortality in the dog. To this observation we should like to add another. We observed repeatedly that partial occlusion of the coronary arteries was better tolerated if the heart had been given a collateral bed at a previous operation. This statement was based on opinion obtained at the operating table, but it has been repeated so frequently that we are willing to present it as fact. On the basis of this evidence the presence of a collateral circulatory bed can be considered as a prophylaxis against the ravages of sudden occlusion of the major coronary arteries.

The experiments showed that vascularization of the myocardium from a collateral bed was slight and in some experiments almost completely absent if the coronary circulation was normal. *In other words, the blood vessels grow into the myocardium when the latter has need for more blood.* On the basis of one observation it would seem that such collaterals can be demonstrated by injection as early as three weeks after the collateral bed has been established.

Total occlusion of a coronary artery can be produced without fibrosis or infarction of the myocardium. In only a few experiments did an infarct supervene, and it may be assumed that the occlusion in these experiments was produced so abruptly that the collateral circulation was inadequate to keep the myocardium viable.

The anastomoses between the cardiac and extracardiac vascular beds were functional. If these vessels had not transmitted blood, infarcts would have been more common than they were. The heart must get a supply of blood from some source to preserve its contractility. For this reason also we believe the direction of flow in the collateral bed is toward the heart rather than away from it. However, it has been observed that under certain circumstances the direction of flow in the anastomosis can be away from the myocardium. Reference to this observation has been given in this paper. Additional evidence in reference to the direction of arterial blood flow in the collateral bed was supplied by the observation that a greater degree of injection in the myocardium was obtained in those regions of the heart from which the coronary artery supply was occluded. It is scarcely conceivable that the direction of the arterial current should be away from such areas of the myocardium poorly supplied with blood.

We found that the normal dog could sometimes, but not always, tolerate a reduction in size of about one-third of both coronary arteries carried out in one stage. With this reduction of the coronary circulation the myocardium remained viable and maintained its power of contractility. The high mortality in our experiments was obtained when a greater degree of constriction than this was used.

Multiple ligation of secondary branches of the right coronary artery, of the ramus descendens, or of the ramus circumflexus was not well tolerated. Peripheral ligations of the arteries was followed by the production of foci in the myocardium that became discolored. These areas undoubtedly lost their property of contractility, and fibrillation frequently followed. It should be pointed out that in the two groups of experiments in which the coronary blood flow was reduced, one by partial central occlusion and the other by peripheral ligation, a greater degree of reduction in the total coronary blood flow seemed to be possible if the occlusion was central than if it was peripheral. In other words, total coronary blood flow is one important factor, but distribution of coronary blood flow is another important factor in reference to survival. There must be an equal distribution of blood to different parts of the myocardium. In this respect peripheral occlusion of coronary arteries may act like a weak link in a chain. We were slow in appreciating this very important fact, and it required a high mortality to demonstrate it to us. We believe the collateral bed was effective in bringing about an even or balanced distribution of blood to various parts of the myocardium. This was accomplished in two ways: (1) by supplying the myocardium with blood from extracardiac sources and (2) by transporting blood from one region of the myocardium that had an adequate blood supply to another region that had a deficient blood supply. The tissues adherent to the heart can act like anastomotic bridges that connect one coronary artery with the other.

We made the observation also that the degree of constriction produced by a silver band around a coronary artery was to a certain extent progressive in degree. Edema and fibrosis at the site of the clip not infrequently led to complete or almost complete occlusion of a vessel within a few days or weeks. This undoubtedly accounted for some of the mortality in the experiments. We confirm the observation of Halsted[5] that the obstruction of a vessel surrounded by a metal band may become progressive and complete. Bands of periosteum placed around the coronary arteries produced scar tissue which did not seem to produce constriction of a progressive nature. Nor did the transplanted periosteum form any bone. The use of a specially molded clip made from sheet silver was found to be more satisfactory for our purpose than any other method. This clip usually could be found at reoperation, and the lumen of the clip could be reduced in successive stages. To help locate the clip at reoperation, a loop of silver wire was placed around the artery adjacent to the clip. Also, the wire could be pulled taut and twisted, and complete closure of an artery could be produced if the clip could not be isolated from the scar. The loop of wire sometimes changed its position so that total occlusion of the artery occurred. Several animals were

lost because of this. However, wire was preferable to silk because the latter lost its tensile strength when buried in the body for several months.

We believe that the epicardium and the endothelial lining of the parietal pericardium may act somewhat as a barrier to the growth of blood vessels into the myocardium. Blood vessels can penetrate the epicardium, but we believe, perhaps without adequate experimental proof, that a richer vascularization is found when pericardial fat is in intimate continuity with muscle fibers. Therefore, we removed the epicardium with special burrs. In some instances the epicardium was stripped from the myocardium in sheets. Extensive removal of the epicardium can produce extrasystoles, tachycardia, dilatation of the heart, and ventricular fibrillation. The heart should be given periods of rest to prevent the summation of these responses. Studies are now being carried out to determine whether or not cocaine or novocaine will block the impulses going into the heart when the epicardium is removed. For the removal of epicardium and endothelial lining of pericardium we found that special burrs were more satisfactory than other methods. It was not necessary to incise the myocardium, nor was it necessary to suture structures to the heart. The vascular bed that developed after removal of epicardium and lining of parietal pericardium did not constrict the heart if the removal of epicardium and endothelial lining of pericardium was done by mechanical methods. Dakin's solution[6] and other chemicals when introduced into the pericardial cavity produced a thick layer of scar tissue which interfered with the heart action. Such solutions should not be used. The question naturally arises as to how much this vascular bed adherent to the myocardium interfered with the motion of the heart. It might be stated that cardiac adhesions per se are usually of little or no significance so far as any demonstrable disturbance to the heart is concerned.* In these experiments the vascular bed could stretch sufficiently to avoid cardiac compression. Adhesions between the vascular bed and the chest wall when present in these experiments did not seem to be of significance, although the heart was not extensively bound to the thoracic wall.

We believe that we have sufficient experimental data to justify their application to human patients. These experiments open an entirely new field and a great many problems present themselves in a most urgent way for study. It would be hazardous perhaps to predict the significance of these experiments at the present stage of development, but we believe that they hold promise of overcoming in an effective way the dreadful mortality from disease of the coronary arteries. In general terms, what we are trying to do is to destroy the "Gleitorgan" effect of

*Cardiac adhesions are usually silent lesions and their importance has been overemphasized. Scar tissue adherent to the heart can disturb the heart in two ways: (1) By its constricting effect producing either acute or chronic cardiac compression. This may be brought about without any adhesions. Adhesions when present in this condition are silent and incidental. (2) By producing a harness of adhesions through which the heart pulls upon the thoracic wall.

the pericardium in order to give the heart additional power to build a collateral blood supply. We believe that many catastrophes inflicted by reduction of a coronary artery could be avoided if the myocardium had direct continuity with another vascular bed. A little blood properly distributed to the area where most needed might preserve the heartbeat, and then as time elapsed the blood supply would be augmented, and vigorous function might again be resumed. We believe our experiments have demonstrated that the collateral bed can become the major source of blood supply to the heart.*

SUMMARY

The heart was given a collateral vascular bed by operation. Almost total occlusion of both coronary arteries was effected with recovery when a collateral vascular bed was present. The significance of these experiments in the treatment of coronary occlusion is discussed.

The illustrations were made by Theodora Bergsland.

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*The first operation of this kind on a human being was performed by us at the Lakeside Hospital Feb. 13, 1935. This patient had coronary occlusion and angina pectoris. An attempt was made to give the heart a new source of blood supply.

THE PRODUCTION OF A COLLATERAL CIRCULATION TO THE HEART

II. Pathological Anatomical Study*

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IN THE preceding paper, it has been shown that extensive anastomoses between the coronary arteries and those of the parietal pericardium and mediastinum develop in surgically produced pericardial adhesions in dogs. It has also been shown that the patency of these anastomoses increases as the normal flow of blood directly from the aorta to the coronary arteries is reduced. These observations make it seem likely that the production of pericardial adhesions offers a means of providing the heart with an effective collateral circulation. If this be true, it would be well to examine the pathological anatomy of coronary disease in man to determine the practicability of the application of this procedure.

Ninety-four human hearts in which a major coronary artery had been occluded were studied. Early in the investigation it was discovered that neither the absence of infarction nor the patency of vessels excluded the possibility of remote major trunk occlusion. Hearts were examined in which old complete occlusion of the major coronary artery was not associated with corresponding infarction. In other hearts, large cicatrized infarcts indicated remote major trunk occlusion, but canalization of the thrombus and enlargement of collateral channels obscured the original site of obstruction. These ninety-four hearts were judged to have sustained major trunk occlusion either because the site of occlusion was identified, as was usually the case, or because the infarct was so large, so uniform in character, and so situated anatomically that despite our inability to determine the exact site of remote occlusion it could be regarded with certainty to have occurred.

The average age of the individuals upon whom this report is based is fifty-four years, and the range was from thirty-five to seventy-nine years. The age distribution does not differ significantly from that reported by other observers (Fig. 1). Men outnumbered women in the ratio of about 3 to 1, and whites outnumbered blacks slightly more than 4 to 1.

Not all of the ninety-four died primarily or solely of coronary occlusion. As shown in Table I, there were seven persons who died of diseases in no way related to coronary disease but who had nevertheless sustained major coronary occlusion. It is obviously not possible to say

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TABLE I

NO. OF CASES	RELATION OF CORONARY OCCLUSION TO DEATH
64	Coronary thrombosis was judged to be principal or sole cause of death.
18	Death from progressive heart failure contributed to coronary occlusion.
5	Death due principally to hypertensive heart disease.
7	Death from miscellaneous causes, not related to primary heart failure.

whether they would have died ultimately of progressive coronary disease or not. Five died of complications due to hypertension, and although post-mortem examination disclosed coronary occlusion, the coro-

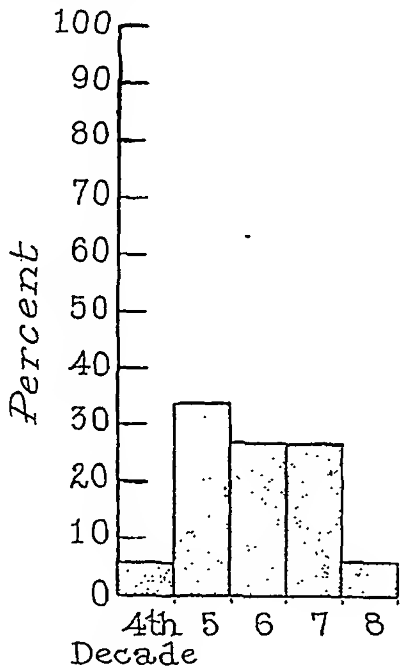

Fig. 1.—Percentile distribution of cases by decades.

nary disease was not judged to have been significant as a cause of death. In eighteen in whom death was due to gradually progressive heart failure associated with severe hypertension, coronary occlusion could not be regarded as the sole or principal cause of death. In sixty-four (68 per cent) of the entire group, coronary occlusion was judged to be the principal or sole cause of death.

Concomitant essential hypertension occurred with greater frequency than is indicated in Table I. There was clinical, pathological, or clinical and pathological evidence of hypertensive heart disease in 52 per cent of the entire group. This figure represents all of the individuals in whom there was anatomical evidence of essential hypertension, but, since detailed clinical records were not available in many instances, the actual incidence of hypertension may have been higher. An individual was

classified as belonging to the hypertensive group if there were repeated blood pressure observations with a systolic over 150 and a diastolic over 100 mm. of mercury, or if the heart weighed in excess of 500 gm. and arteriolar disease was present. Five hundred grams was arbitrarily selected as the maximum heart weight in the nonhypertensive group because it was found that in a number of instances in which hypertension was not observed on repeated clinical examination, during periods of

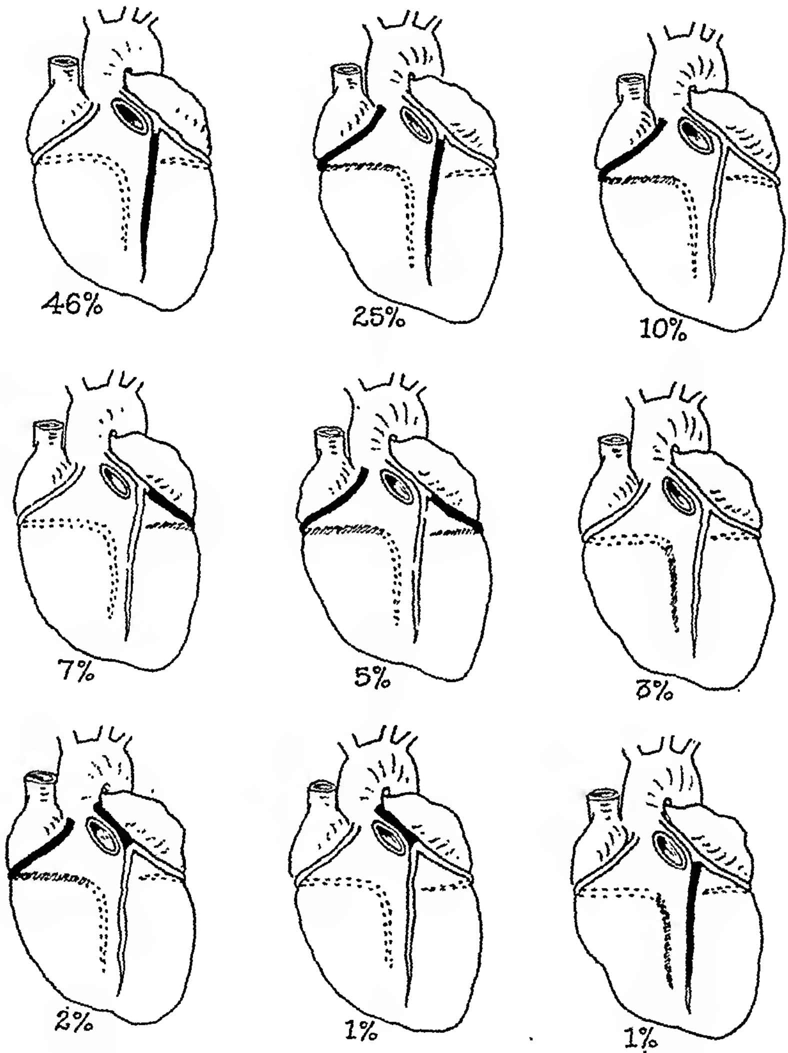

Fig. 2.—Percentile frequency of various sites of coronary arterial occlusion.

cardiac competence, and in which there was no disease of the smaller arteries, heart weights up to 500 grams occurred. It seemed likely therefore that the dilatation incident to myocardial ischemia predisposed in some instances to cardiac hypertrophy. It is of interest that the concomitant occurrence of essential hypertension and coronary occlusion was especially high in women (86 per cent) and in negroes (88 per cent).

The left coronary artery only was occluded in 54 per cent, the right only in 13 per cent, and both left and right in 33 per cent. Fig. 2

shows the sites of coronary occlusion. The divisions of the arteries most commonly occluded were the descending ramus of the left (72 per cent), the circumflex portion of the right (42 per cent), and the circumflex portion of the left (12 per cent).

It may be seen in Fig. 3 that the percentile incidence of left coronary occlusion decreased with age, with a corresponding increase in the relative percentages of right and of bilateral coronary occlusion. In those persons who lived beyond the age of sixty years there was less disparity between the numbers of right and left coronary occlusions and a relatively greater number of bilateral occlusions than present in the younger age periods. There was no significant difference between right

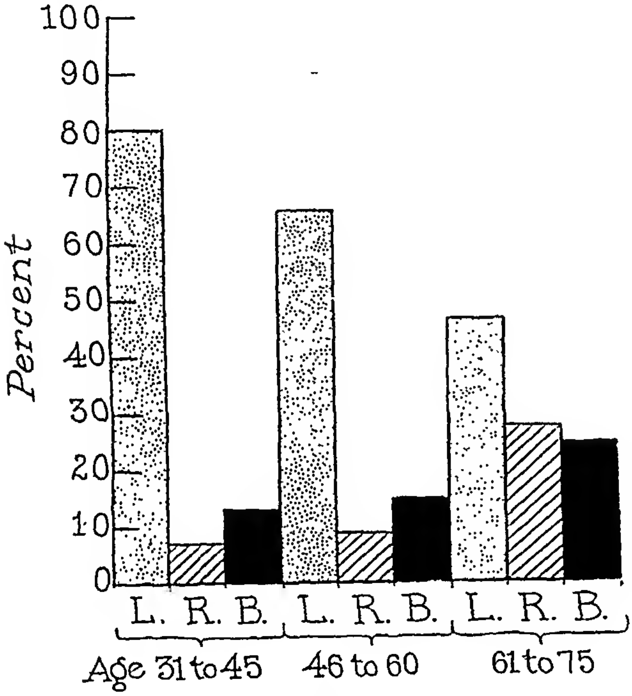

Fig. 3.

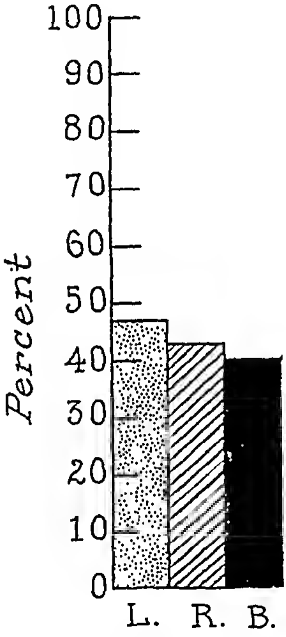

Fig. 4.

Fig. 3.—Percentile incidence of arteries occluded in each age group. (*L*, left coronary; *R*, right coronary; *B*, both.)

Fig. 4.—Percentile incidence of sudden death in cases of coronary thrombosis, in relation to artery occluded. (*L*, left coronary; *R*, right coronary; *B*, both.)

and left coronary arterial occlusion in relation to the occurrence of sudden death, and bilateral coronary occlusion was not associated with an increase in the occurrence of sudden death (Fig. 4).

The explanation of the increasing incidence of right coronary occlusion with age was not apparent. No figures were available for us to determine whether or not this is in accord with the findings of other observers. A study of the cases of bilateral coronary occlusion revealed that in all but five of the thirty-one cases the occlusions had not occurred simultaneously. The first occlusion, which had occurred with about equal frequency in the right and left coronary arteries, had developed

so slowly that the corresponding infarcts were not as extensive as would be expected considering the normal distribution of the vessel below the point of occlusion.

Despite the fact that the incidence of bilateral coronary occlusion increased with age, the incidence of sudden unexpected death from coronary occlusion decreased with age. Death was regarded as sudden when the period of cardiac invalidism was less than one week in duration. Fig. 5 reveals a sharp decline in the incidence of sudden death with increasing age. This is in accord with the observations of Conner and Holt.[1]

A plausible explanation of this apparent contradiction between the increased incidence of severe and extensive coronary sclerosis and the corresponding decreased incidence of sudden death from coronary occlusion is that the severity of the chronic myocardial ischemia probably determines cardiac incompetence before the terminal thrombosis occurs.

Of the ninety-four individuals in whom one or more coronary arteries were obstructed, only fourteen died following the first occlusion, and only eight of the fourteen died of uncomplicated coronary thrombosis. If these ninety-four individuals can be considered representative, it would appear that the majority (86 per cent) survive the first coronary occlusion. Moreover, in most of these (70 per cent of the entire group) there had been a period of cardiac competence varying greatly in duration after the primary occlusion. The significance of these observations in relation to the practicability of artificially inducing a collateral coronary circulation is obvious. The fact that 70 per cent of all persons having a major coronary occlusion not only survived the occlusion but had a subsequent period of myocardial competence would imply that most cases of occlusive coronary disease can be recognized as such. This is in accord with the studies of Wearn,[6] Levine and Brown,[4] and Conner and Holt. Furthermore, the disease is commonly recognizable before such extensive myocardial damage has been sustained as to determine chronic cardiac invalidism. In 117 cases Conner and Holt report a survival of only 21 per cent in a state of good health for more than five years after the first attack.

There is reason then to believe that relatively few (21 per cent) of the large number of individuals with occlusive coronary disease which can be recognized as such during good health escape cardiac invalidism longer than five years after their first attack. It cannot be said that all of those who die do so because of myocardial ischemia alone. In our series of cases 68 per cent of the entire group died of this cause.

Death in these individuals was commonly the result of additional coronary thrombosis with presumably such a concomitant increase in severity of coronary sclerosis that collateral circulation was no longer

adequate or because there was already such extensive myocardial obstruction that more was incompatible with circulatory competence.

There is abundant evidence that the coronaries are not end arteries but anastomose freely with one another (Gross[2] and Spalteholz[5]). In the event of the occlusion of a vessel which supplies so much of the heart, or such portions of the heart that complete ischemia would be incompatible with life, the physiological effects are determined by a combination of circumstances. The extent of the myocardial damage and, *pari passu*, the seriousness of the functional disturbance depend upon the suddenness of the occlusion, the patency of the collateral channels, and upon the blood pressure.

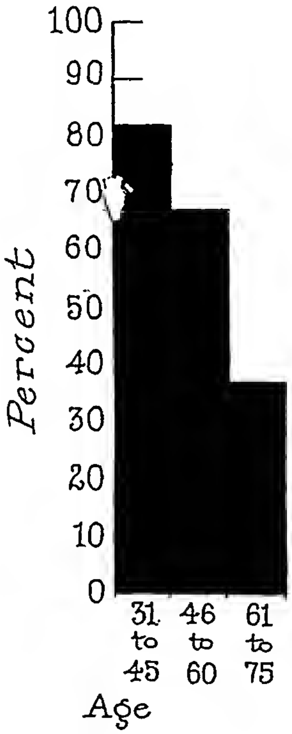

Fig. 5.—Percentile incidence of sudden death due to coronary occlusion, in relation to age.

Anatomically, two types of collateral channels develop in the dog as a result of surgically induced pericardial adhesions, and the same type of anastomoses might reasonably be expected to develop in man. The superficial anastomoses between the coronary arteries in the epicardium are increased, and the epicardial barrier between the coronary arteries and the arteries of the parietal pericardium and mediastinum is destroyed so that anastomoses between them occur. On anatomical grounds it would appear likely that such anastomoses would serve to protect the heart against the failure of collateral coronary circulation that usually determines death. Obviously such a collateral circulation could not be effective if there were significant coronary disease in the arteries

within the substance of the myocardium. Microscopical examination of many blocks from the myocardium in this group of cases indicated that significant sclerosis of the penetrating myocardial vessels was the exception rather than the rule. This is in accord with the opinion expressed by Karsner:[3] "The lesion appears to progress with diminishing severity from larger to smaller branches." The significant sclerosis and thrombosis were commonly confined to the superficial vessels, and the superficial vessels are the ones to which a collateral circulation by means of pericardial adhesions would be made available.

SUMMARY

On the assumption that thrombotic occlusion of a major coronary artery can be recognized clinically, it is probable that the diagnosis could have been made in life in eighty of these ninety-four patients. Only fourteen patients died as the direct result of the first major coronary occlusion. Of the eighty patients who survived the first occlusion, the question is whether or not they could have been protected against disastrous results from subsequent occlusions by the production of extracardiac coronary collateral circulation.

In thirty-seven of these eighty cases, concomitant disease or continued cardiac incompetence rendered the operative risk unjustifiable. The remaining forty-three patients might have been benefited by the production of the additional collateral circulation. With the exception of seven patients, who died of other causes, all died of subsequent attacks of coronary thrombosis.

This data, chiefly pathological, derived from this study of ninety-four cases of major coronary arterial occlusion would indicate that there was a period after the first coronary occlusion in the lives of forty-three individuals when the production of extracardiac coronary collateral circulation might have been feasible and beneficial.

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THE PRECORDIAL LEAD OF THE ELECTROCARDIOGRAM (LEAD IV) AS AN AID IN THE RECOGNITION OF ACTIVE CARDITIS IN RHEUMATIC FEVER*

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In the management of the patient with rheumatic fever, the most important clinical problem which presents itself is the recognition of active cardiac involvement. Bedside observation is sometimes adequate for decisive diagnosis. A count of the leucocytes and determination of the sedimentation rate of the red blood cells often furnish helpful information. Serial electrocardiography, with employment of the three standard leads, has proved to be a valuable method for following the effect of the rheumatic process on the heart.[1] We have found that the additional use of Lead IV has, in certain instances, revealed evidence of active carditis when, in the usual three derivations, either no changes in form were apparent in successive records or the alterations noted were regarded as equivocal.[2]

The use of chest leads in the study of the physiology of the heart is not a novel procedure. In his original work with the capillary electrometer, Waller[3] in 1887 placed the electrodes directly on the chest wall. The studies of Lewis, Drury, and Iliescu[4] on auricular fibrillation and flutter in man were materially furthered by the application of this method. It was Wolferth and Wood,[5] however, in 1932, who awakened interest in the use of chest leads for clinical purposes by demonstrating their value in the diagnosis of coronary occlusion. With the exception of our own preliminary note,[2] we have not seen any previous report on the use of Lead IV as an aid in the recognition of active myocardial involvement in rheumatic fever and in following its course.

In recording Lead IV, a stiff, rubber-covered spring was employed to retain in position two flat German silver discs, each 3 inches in diameter and fitted to receive the terminals of the lead wires. The skin at the sites of application was rubbed vigorously, first with alcohol, then with salt solution. The discs were covered with heavy flannel jackets saturated with warm saline. The resistance of the skin was usually under 2,000 ohms. Curves showing overshooting were discarded. The patient reclined on his back, either in the recumbent or semirecumbent position. The same posture was always assumed by any given patient when successive records were being made. The anterior (right arm) electrode was placed just to the left of the sternum, with its center approximately

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in the fourth interspace. The posterior (left arm) electrode was placed at a corresponding level in the back, to the left of the spine. Care was taken to place the anterior electrode always in the same position since a shift may vary the contour of the record obtained.[6] Slight shifts in the position of the posterior electrode are of little importance.*

Changes in the form of Lead IV which were considered to be abnormal were: an upright T-wave,† a negative T-wave deeper than 9 mm., a monophasic or notched QRS group, an R-T or S-T segment above the isoelectric line or one that was more than 2 mm. below this level.[7, 8] Any changes in form occurring in records taken on the same patient at different times were regarded as indicating alterations in the state of the myocardium. Such successive changes, however, while they show that the heart is affected and that the lesions are not in a quiescent state, are not specific for rheumatic fever.

Bed Patients.—Observations were made on thirty-eight patients with rheumatic fever in the wards of the hospital. None was taking digitalis or quinidine although a majority was receiving salicylate or pyramidon. Two hundred and ten electrocardiograms were made. By far the most frequently observed changes in Lead IV were alterations in the direction or voltage of the T-wave. In this series no example of elevation of the R-T or S-T segment occurred. The alterations in T_4 frequently appeared to indicate not only that changes were taking place in the heart muscle, but also the direction of the change as well. When the clinical condition of a patient suggested continued or renewed activity of the rheumatic process, this wave tended to assume an abnormal contour. When, on the other hand, other signs indicated healing of the rheumatic lesions in the heart, it generally approached or resumed the normal shape (Fig. 1).

In seven cases a change was noted in Lead IV only (Fig. 2). In sixteen cases changes were observed in the three standard leads as well as in Lead IV (Fig. 3); but in a number of these records significance could be attributed to minor variations in the first three leads, especially slight changes in the T-wave in Lead III, by finding gross alterations in Lead IV (Fig. 4).

In five cases changes were observed in the three standard leads, whereas the contour of Lead IV was not affected. Under these conditions the alterations in the first three leads consisted either of variations in auriculoventricular conduction time or of well-defined changes in the T-wave in Lead III. In ten cases no changes were seen in any lead.

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*Since this work was completed, it has become our custom to use small, direct-contact metal electrodes and a saline jelly. The right arm electrode is placed on the precordium, as here described. The electrode on the left leg serves as the indifferent terminal. The complexes recorded in this way differ slightly in form from those obtained by the anteroposterior technic. But the criteria for normality and the character of the changes observed are the same.

†An upright T-wave in Lead IV has been observed in a number of normal children under twelve years of age. However, changes occurring in successive records retain their significance with respect to denoting alterations in the state of the heart muscle.

The series is small and no significance is attached to the relative number of cases in which each of these occurrences was noted. It is striking, however, that in twenty-three of thirty-eight cases the appearance of Lead IV was either the sole electrocardiographic index of active myocardial involvement or was important in confirming suggestive evidence supplied by the three standard derivations. It seems likely that had electrocardiograms been taken at more frequent intervals, the incidence of changes indicative of cardiac involvement would have been higher.

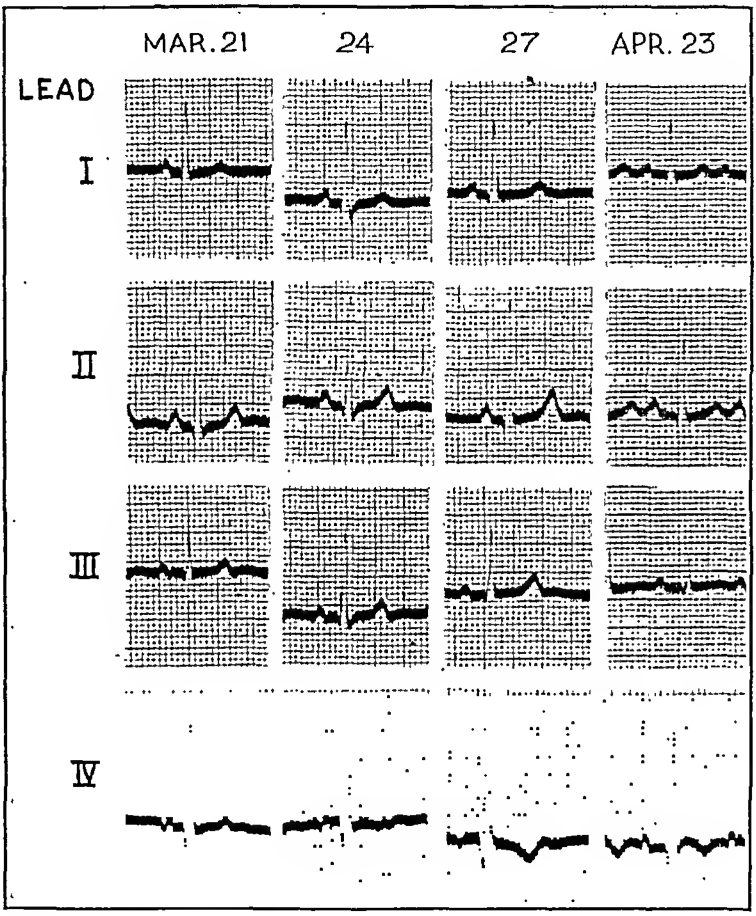

Fig. 1.—D. H., female, aged twenty-five years, was admitted March 20. She had attacks of rheumatic fever at eight and sixteen years of age with mild, recurring joint pains since. She bore two children without cardiac symptoms. Two months ago a heart murmur was heard. Two weeks before admission she had quinsy, followed soon after by severe joint pains and a rash.

On admission: Temperature, 98.8° F.; pulse, 100; blood pressure, 114/44. Heart enlarged; mitral systolic and diastolic murmurs. Typical erythema nodosum over arms and legs. *March 21:* Temperature, 101.4° F.; W.B.C., 16,200 with 76 per cent polymorphonuclears; Sedimentation rate, 87. Electrocardiogram: sinus rhythm; rate, 80; P-R, 0.16 second; T_4, upright. Aspirin, 3 gm. on this day. *March 24:* Temperature, 100° F. Joint pains less intense and erythema subsiding. Electrocardiogram: Rate, 85; P-R, 0.16 second; slight changes in the R-T segment in all leads; T_4, diphasic. *March 27:* Temperature, 100.2° F. Electrocardiogram: rate, 70; P-R, 0.16 second. Again slight changes in the R-T segment in all leads; T_4 at this time sharply inverted. *April 9-14:* Five teeth extracted, following which operation the [illegible] W.B.C., 11,700, with 80 per cent polymorphonuclears. [illegible] *April 23:* Aches and pains in the legs, shoulders, back, and [illegible]: sinus tachycardia; rate, 105; P-R, 0.20 second. The [illegible] was reactivated following extraction of teeth. T-wave changes in all leads; P_4, upright; T_4, diphasic, with striking change in the contour of the R-T segment. *May 2:* Sent to convalescent home.

Ambulatory Patients.—A single record only was taken of thirty-four ambulatory patients with rheumatic heart disease who came to the Vanderbilt Clinic. In eight, deviations from the normal were observed in Lead IV only. In seven, changes were seen in the three standard leads, as well as in Lead IV. In eleven, changes were observed in the three standard leads and not in Lead IV. In eighteen, no changes were recorded in any lead. Single records of Lead IV on patients with rheumatic heart disease have been taken by others.[7, 9] Obviously, it is not possible, on the basis of only one electrocardiogram, to establish the presence of active carditis. Abnormalities, if present, merely indicate that the myocardium has been damaged.

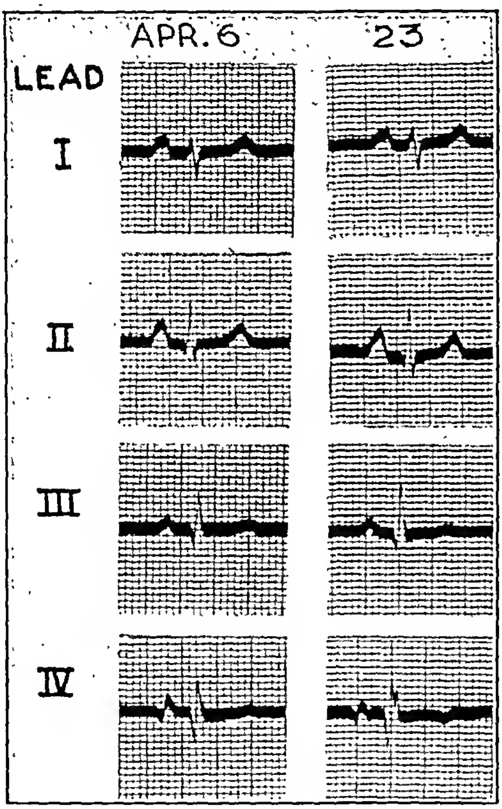

Fig. 2.—R. K., female, aged twenty-four years, was admitted April 4. She had rheumatic fever at the age of twelve years, with no known cardiac involvement. Polyarthritis recurred three months before admission and confined her to bed for a month. Since, she has noted dyspnea on exertion.

On admission: Temperature, 98.8° F.; heart rate, 80; blood pressure, 116/68. She was thin and pale. Heart enlarged. Signs of mitral and aortic valvular disease, with congestive failure. *April 6:* Temperature, 99.6° F.; W.B.C., 8,300, with 73 per cent polymorphonuclears. Sedimentation rate, 24. No drugs given. Electrocardiogram: sinus rhythm; rate, 65; P-R, 0.20 second; right ventricular preponderance; T_4, upright. *April 23:* Great improvement; patient very comfortable. Temperature, 99° F.; W.B.C., 6,500, with 65 per cent polymorphonuclears. Sedimentation rate, 23. No drugs. Electrocardiogram: rate 64; P-R, 0.20 second. First three leads similar in appearance to those observed April 6. Lead IV showed marked notching of QRS and inverted T-wave. *April 27:* Patient sent to convalescent home. *May 10:* Patient died in Peekskill Hospital. Report stated that she had heart-block.

Autopsy Cases.—Post-mortem examinations were made on seven additional patients observed in the hospital. In none had changes been noted in Lead IV only. In four, changes were seen in the first three leads, and

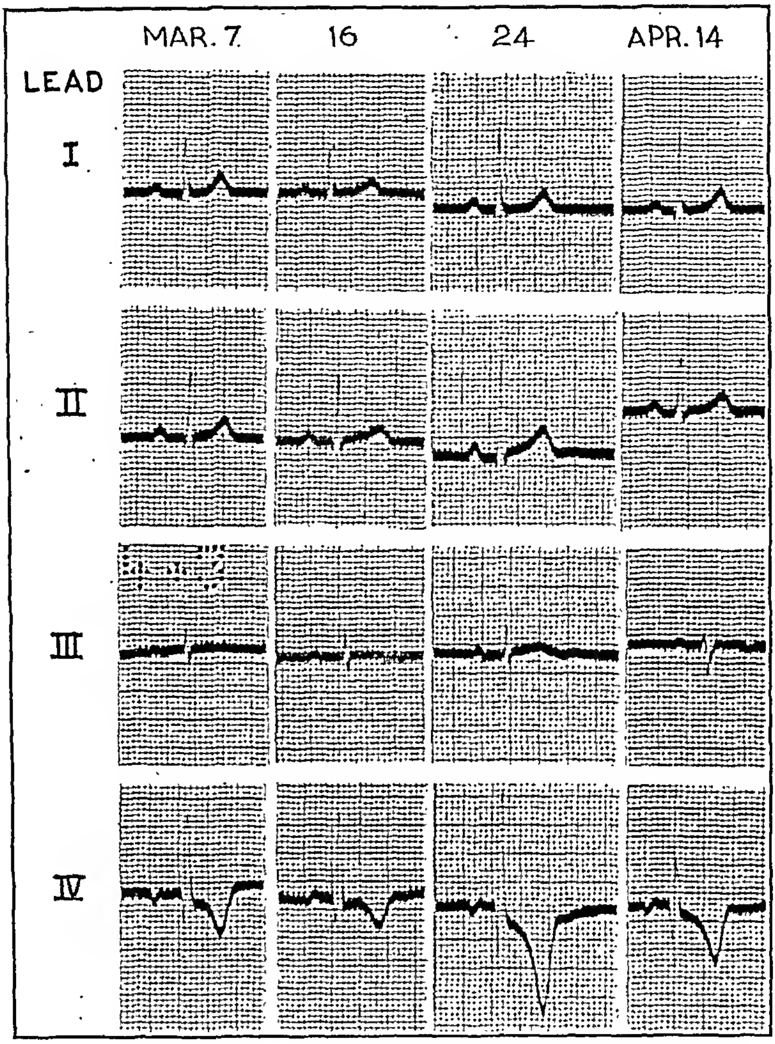

Fig. 3.—V. S. P., male, aged twenty-five years, was admitted March 6. He had two previous attacks of rheumatic fever, the first fourteen years, and the second nine years prior to admission, each lasting for several months. There were no cardiac symptoms. He complained of pain and swelling in various joints for one week.

On admission Temperature 103° F.; pulse, 84; blood pressure, 110/70. Tonsils large. Heart slightly enlarged. Systolic murmur at apex. All joints of arms and legs affected. W.B.C., 18,200. Throat culture yielded hemolytic streptococcus. *March 7:* Temperature, 103.2° F.; W.B.C., 17,900, with 85 per cent polymorphonuclears. Well-marked secondary anemia. Sedimentation rate, 45. Aspirin, 3.6 gm. on this day. Electrocardiogram: sinus rhythm; rate, 80; prolonged conduction, with P-R, 0.22 second. No changes in form. *March 16:* Temperature, 99.4° F. More comfortable. W.B.C., 18,000; sedimentation rate 48. Aspirin, 7.5 gm. on this day. Electrocardiogram: rate, 60; P-R, still 0.22 second; R-T segment, slightly elevated in Leads II and III; T_1 and T_2, slightly lower; T_4, less deeply inverted, with greater convexity of R-T segment. *March 24:* Temperature, 99.2° F.; W.B.C., 9,000, with 74 per cent polymorphonuclears. Sedimentation rate, 17. Aspirin, 9 gm. on this day. Electrocardiogram; rate, 55; P-R, 0.19 second; T-waves, higher in the first three leads, with elevation of the R-T segment in Leads II and III. In Lead IV, T-wave, deeply inverted, measuring 14 mm.; R-T segment, depressed. The voltage in Lead IV had become greater, but this is not due to overshooting, for the resistance was 900 ohms. *April 14:* Temperature, 99° F.; systolic murmur at apex persisted. Pyramidon, 3.6 gm. on this day. Electrocardiogram: rate, 55; P-R, 0.19 second; T_2, lower; S_3, deeper. R-T segment in Lead III, less sharply elevated. In Lead IV, T-wave, less deeply inverted. R-T segment, no longer significantly depressed. *May 11:* Patient discharged from hospital.

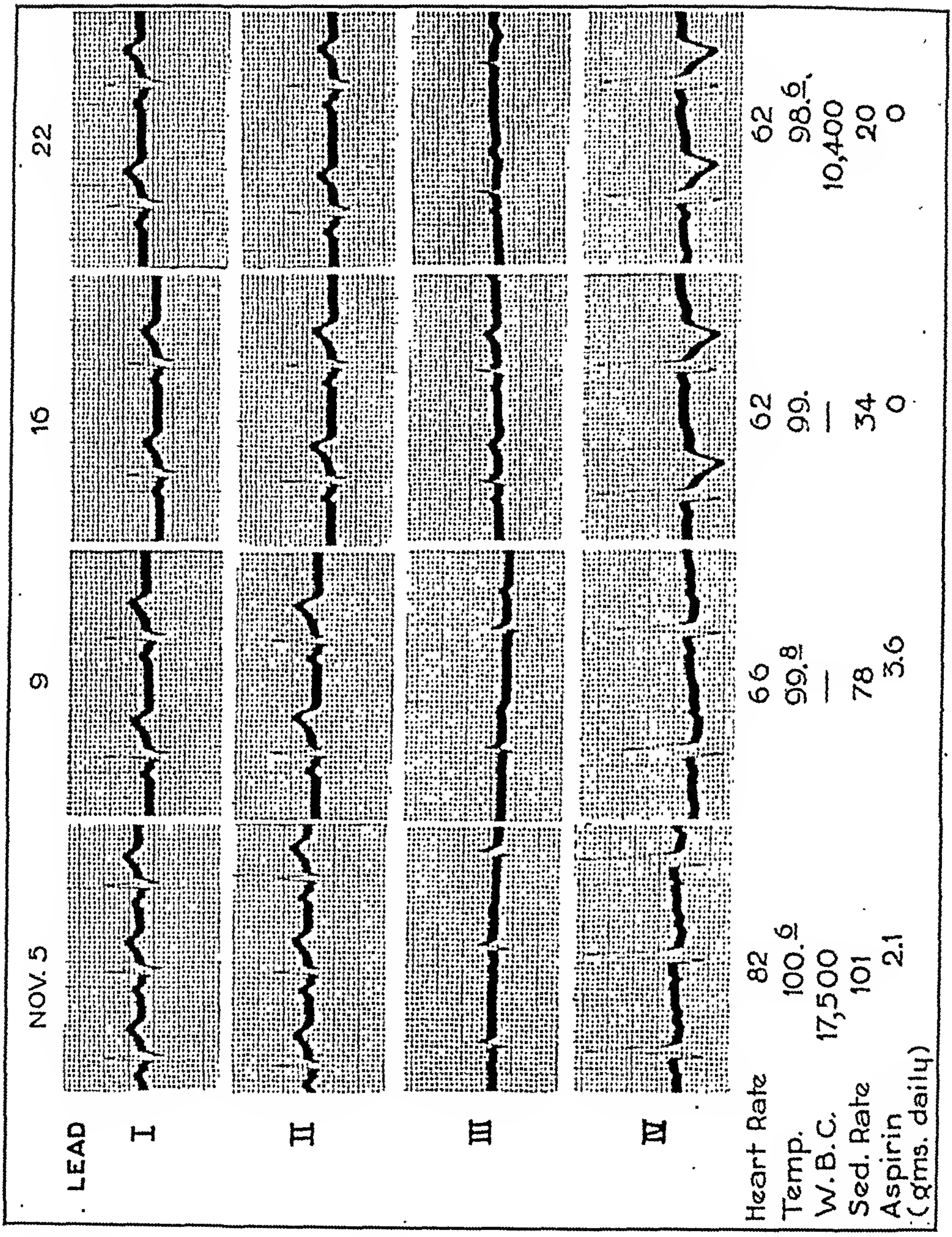

Fig. 4.—C. H., male, aged twenty-nine years, was admitted November 4. He had rheumatic fever at the age of twenty-two years and was in bed for three months, but there was no known cardiac involvement. An apical systolic murmur was first heard a year before admission. Nine days before admission he had a sore throat, followed six days later by mild joint pains and a temperature of 103° F.

On admis[illegible] *olic blow at apex. Blood pressure, 140/90. *November 5* [illegible] second; T_4, diphasic. *November 9:* Patient more [illegible]: P-R, 0.14 second. T_2 and T_3, a little higher. Ver[illegible] *November 16:* Electrocardiogram: P-R, 0.15 second; slight changes in the form of R and T in Lead III; marked alteration in T_4 with return toward normal contour. *November 22:* Patient very comfortable. Elec[illegible] Again slight change in T_3. Lead IV as in previous [illegible] ischarged from hospital. *December 19:* Patient re[illegible] similar to the one of November 22.

the T-wave in Lead IV was upright. In three of these cases numerous Aschoff bodies were observed in the heart muscle; in the fourth, acute fibrinous pericarditis established the presence of active rheumatic fever although no Aschoff bodies were found. In the fifth case the three standard leads showed changes, whereas Lead IV was normal. In this patient, acute rheumatic pancarditis was present. In the two remaining patients, active rheumatic heart disease was suspected during life, but no changes were present in any of the four leads of the electrocardiogram. In neither instance were Aschoff bodies found at autopsy. One proved to be an example of verrucous endarteritis associated with quiescent valvular lesions; the other was a case of gonococcal endocarditis superimposed upon old, but inactive, rheumatic heart disease.

SUMMARY

1. In rheumatic fever, if successive electrocardiograms are taken, Lead IV may furnish evidence of active carditis when changes indicating active myocardial involvement are not observed in the standard three leads.

2. Frequently, gross variations in the contour of Lead IV indicate the significance of minor alterations in the three standard leads which might otherwise be regarded as of doubtful importance. This statement applies particularly to slight changes in the T-wave in Lead III.

3. On occasion, changes denoting rheumatic lesions in the heart muscle are present in the first three leads when no change is apparent in Lead IV.

4. In ambulatory patients with rheumatic heart disease, a single electrocardiogram may reveal evidence of myocardial damage in Lead IV only. On the basis of a single record, however, it is clearly not possible to establish the presence of rheumatic activity in the heart.

5. Changes in the electrocardiogram characteristic of myocardial involvement were found in five patients whose hearts at autopsy showed lesions of active rheumatism. In two patients, in whom active rheumatic carditis was suspected during life but was not found at autopsy, the electrocardiograms were normal.

6. In rheumatic fever the use of Lead IV is of clinical value as an aid in the recognition of active myocardial involvement and in following its course.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION*

II.† The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery

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INTRODUCTION

When one of the larger arteries of the human heart is suddenly occluded, the ventricular complex of the electrocardiogram undergoes a remarkable series of changes in form. Regarding the origin of these changes, which involve the QRS group as well as the RS-T segment and T deflection, there has been a great deal of speculation, and many different views as to the mechanism of their production have been expressed. A better knowledge of the factors that determine the form of the electrocardiogram in coronary occlusion will not only be of great service in the diagnosis of this condition, but will also help us to understand and to interpret the electrocardiographic abnormalities that occur in other types of heart disease.

The experiments upon which this series of articles is based were prompted by the discovery that infarction of the anterior wall of the human heart produces very striking and distinctive changes in the form of the initial ventricular deflections of precordial leads. Previous observations had shown that the ventricular complexes of such leads are similar in general outline to those obtained by leading directly from the anterior surface of the heart. We concluded that the use of direct and semidirect leads in experimental coronary occlusion could not fail to throw a great deal of light upon the questions at issue.

A full account of the principal methods employed in our experiments, which were carried out on large dogs, has been given elsewhere.[2, 4] Standard Lead I was taken simultaneously with all semidirect and direct leads and is represented by the upper curve in all records. The special leads were taken with a vacuum tube in the galvanometer circuit,[5] and the connections were so made that negativity of the exploring electrode produced an upward deflection. This electrode consisted of a small glass tube stoppered with salted kaolin, in which a short wick or a small piece

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†The first article of this series was published in the Am. Heart J., 9: 596, 1934. The observations reported here were briefly described in a preliminary report[1], and were also referred to in a paper read at a meeting of the Association of American Physicians[2]. Wood and Wolferth[3] have made a somewhat similar study.

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of sponge was embedded, and filled with a solution of sodium chloride. In this solution a silver wire coated with silver chloride was immersed. The indifferent electrode was of similar construction and was placed in contact with the subcutaneous tissues of the left hind leg. The sensitivity of the galvanometer was adjusted to give a deflection of 1 cm. for 20 millivolts when taking direct leads, and a deflection of 3 cm. for 20 millivolts when taking semidirect leads.

In describing our results, it is convenient to speak of the earlier and the later stages of myocardial infarction, the former term being used to designate those stages of the process that precede and the latter those that follow death of the fatally injured muscle. In this article we shall, for

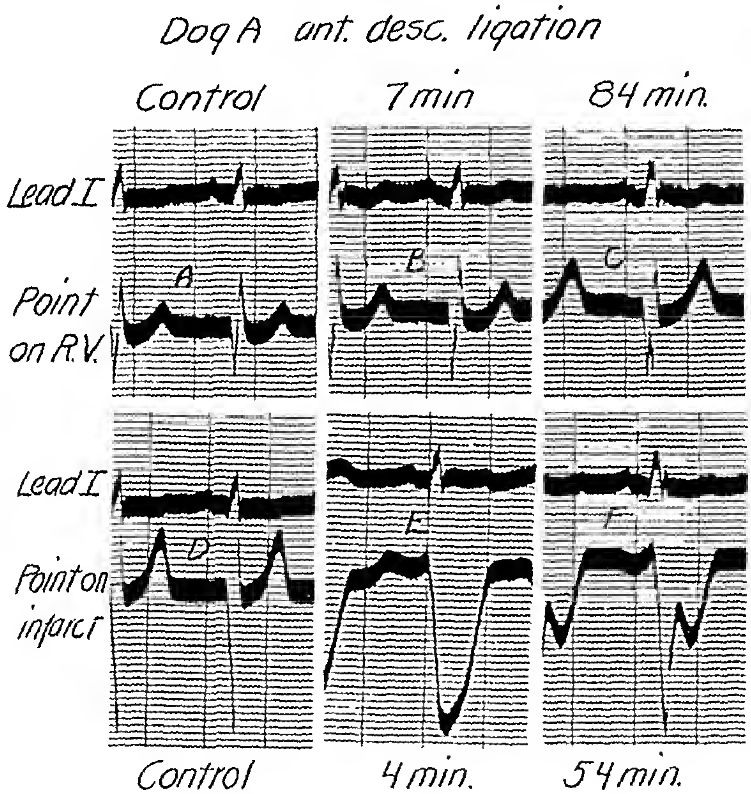

Fig. 1.—Experiment I (Dog A). The lower curve of each record represents a direct lead from the anterior surface of the exposed heart. In the upper row this curve is from a point near the base of the right ventricle, in the lower row from a point near the apex of the left ventricle. *A* and *D* are control curves; the time after ligation when the other curves were taken is indicated. In the direct leads a deflection of 1 cm. represents a potential difference of 20 mv. In this and all other figures the upper curve of each record represents standard Lead I.

the most part, confine our attention to the electrocardiographic changes that occur during the period immediately following coronary ligation.

DESCRIPTION OF EXPERIMENTS

Experiment I (Dog A).—Direct leads were taken from twelve different points widely distributed over the anterior surface of the exposed ventricles. The heart was then covered with a gauze pad (1 cm. in thickness) soaked in normal salt solution (0.9 per cent NaCl), and a series of four semidirect leads was obtained by placing the exploring electrode in contact with the pad. For the first of these

leads this electrode was placed upon the part of the pad which lay upon the base of the right ventricle; with each succeeding lead it was moved about 2 cm. nearer the apex. Neither the direct nor the pad curves showed anything unusual; the latter are reproduced in Fig. 2 (*A*, *B*, *C*, and *D*); and two of the former, one from a point on the base of the right and the other from a point near the apex of the left ventricle, in Fig. 1 (*A* and *D*).

After these preliminary observations the anterior descending branch of the left coronary artery was ligated at a point just distal to the origin of the artery which courses down the lateral margin of the left ventricle. The experiment was com-

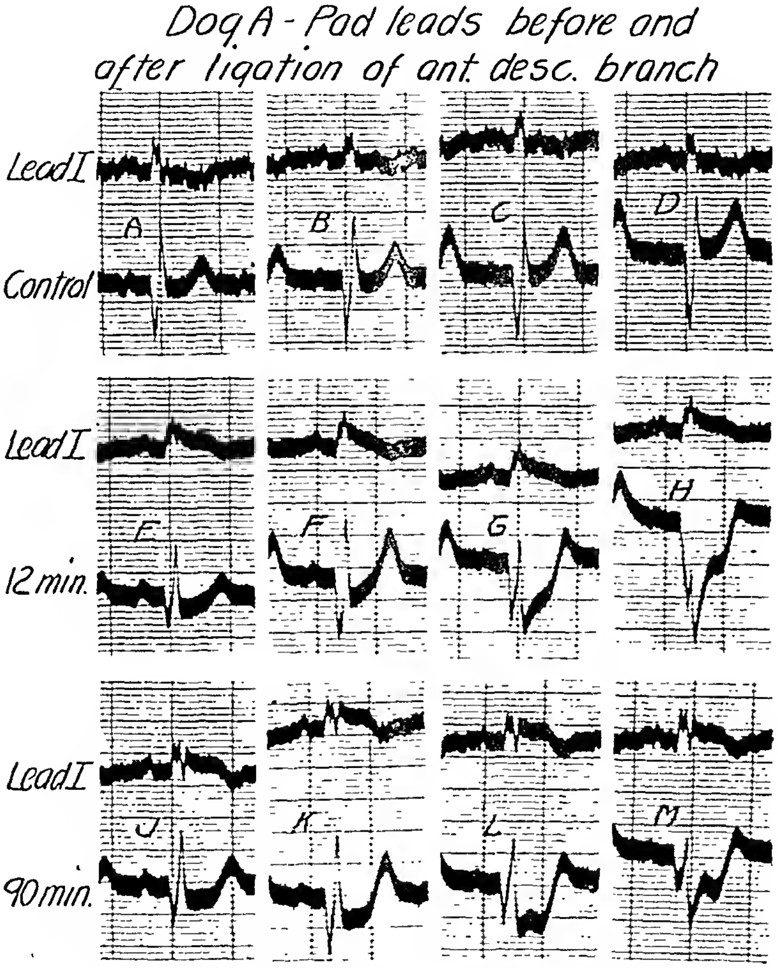

Fig. 2.—Experiment I (Dog A). Semidirect leads taken from a pad laid upon the exposed heart. In these leads a deflection of 3 cm. represents a potential difference of 20 mv.

pleted by taking direct leads from the points previously explored and additional sets of pad leads at intervals during a period of about one and one-half hours.

Within a few minutes the ventricular complexes of the direct leads from the region supplied by the ligated vessel and of the semidirect leads from that portion of the pad overlying this region were transformed into curves that are practically monophasic. This change is well illustrated by the curve shown in Fig. 1*E* which represents a direct lead from the central part of the affected region four minutes after the ligature was tied. This curve is characterized by the presence of a small initial summit, not present in the control curve (Fig. 1*D*) from the same point, and by

complete fusion of QRS and T into a single broad downward deflection. The sharp intrinsic upstroke of the control curve has completely disappeared. The curve from the same point taken fifty-four minutes after the ligation (Fig. 1*F*) is somewhat similar in outline, but downward displacement of the RS-T segment is much less pronounced, and there is a sharp upward movement which apparently represents the intrinsic deflection, reduced in amplitude and occurring between 0.02 and 0.03 second later than in the control curve.

The changes that took place in the curve from the apical portion of the pad were similar. In this case, however, no initial summit developed (Fig. 2*H* and *M*), and the displacement of the RS-T segment was somewhat less pronounced. The sharp upstroke of the control curve (Fig. 2*D*) is not clearly represented in the curves taken after ligation.

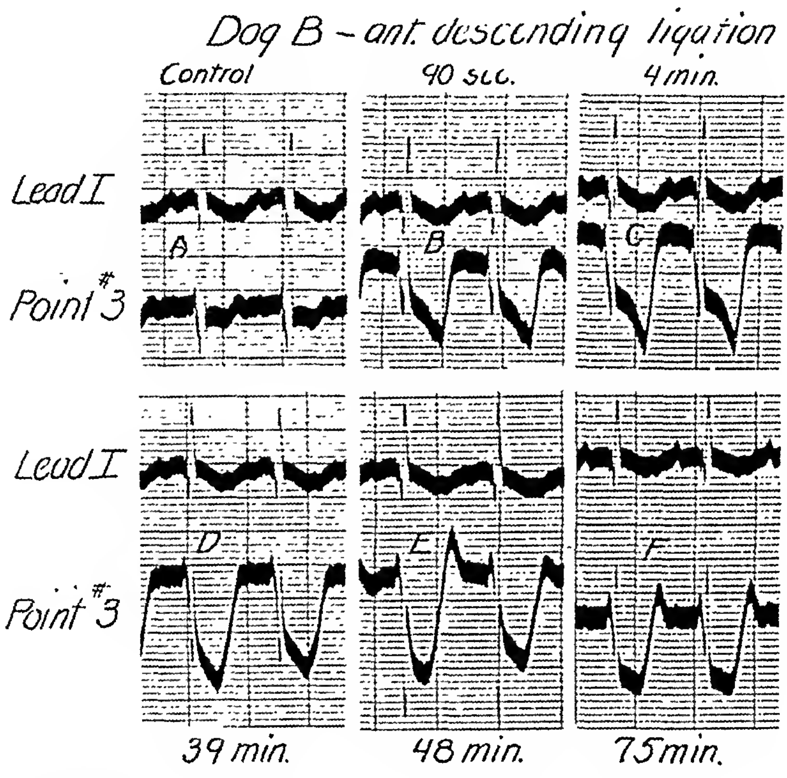

Fig. 3.—Experiment II (Dog B). Direct leads from a point on the left ventricle before and at intervals after the ligation of the terminal portion of the anterior descending branch of the left coronary artery.

Upon the form of the ventricular complexes of the direct lead from the base of the right ventricle, which receives its blood supply from the right coronary artery, and upon the complexes of the corresponding pad curve, the ligation had very little effect. In the case of the direct lead there was some increase in the size of the T deflection, and the initial deflections became conspicuously notched, but the significance of these minor changes under the circumstances obtaining is uncertain.

In the third pad lead the ligation was followed by definite downward displacement of the RS-T segment and by a reduction in the amplitude of the chief upstroke, which corresponds to the intrinsic deflection of direct leads. In the second pad lead there was slight downward displacement of the RS-T segment but no other striking change. In the direct leads from the marginal portions of the region supplied by the ligated vessel, the changes in the form of the ventricular complex were similar to those that took place in the third pad lead. It should be pointed

out, however, that in direct leads conspicuous downward displacement of the RS-T segment often occurs as a result of injury to the heart's surface produced by the application of the exploring electrode or by the continued pressure which it exerts. Such injury is particularly likely to occur when an electrode is applied to the surface of the exposed right ventricle whose anterior wall is continually in violent motion. From some portions of this chamber it is often exceedingly difficult to secure direct curves that are free of injury effects.

Experiment II (Dog B).—After exposing the heart in the usual way, a series of direct leads from the anterior surface was taken. The curves obtained were in no way unusual. One of these leads was from a point near the apex and midway between two small arteries which joined about one centimeter higher up to form the main trunk of the anterior descending branch of the left coronary artery. Several additional curves were taken from this point, and a loose ligature was then placed just above the junction of the arteries on either side of it. A curve from this same point was taken just before and another immediately after the ligature was pulled tight. Others were taken, first at shorter and later at longer intervals, over a period of about five hours. At the end of this time the animal died, apparently as a result of the prolonged anesthesia and artificial respiration. When the heart was removed, the infarcted region was plainly visible, particularly on the endocardial surface where it appeared as a pale area, some two or two and one-half centimeters in diameter, surrounding and involving the base of the anterior papillary muscle of the left ventricle.

All of the control curves from the point specified are similar, and all show a small initial summit (Fig. 3*A*). Ninety seconds after the ligature was tightened, there was already conspicuous downward displacement of the RS-T segment (Fig. 3*B*), but the deflections of the QRS group were not altered. During the next few minutes the RS-T displacement increased, and a definite reduction in the amplitude of the intrinsic deflection took place. In the later curves there was also some increase in the prominence of the initial upward movement. Forty-eight minutes after the ligation there was pronounced alternation in the form of the ventricular complex, and at this time a conspicuous summit at the end of the ventricular complex made its first appearance (Fig. 3*E*). Although the curves taken still later vary with respect to details, they are all similar in general outline to the curve shown in Fig. 2*F*, which was taken seventy-five minutes after the ligature was tied.

TABLE I

TIME OF ONSET AND AMPLITUDE OF THE INTRINSIC DEFLECTION IN EXPERIMENT II

TIME AFTER LIGATION	ONSET OF INTRINSIC DEFLECTION (SECONDS)	SIZE OF INTRINSIC DEFLECTION (MILLIVOLTS)
Control	0.003	54
90 sec.	0.001	60
110 sec.	0.002	54
3 min.	0.007	42
4 min.	0.009	40
39 min.	0.012	28
48 min.	0.013	34
75 min.	0.007	26
95 min.	0.007	34
2 hr.	0.009	36
2 hr. 23 min.	0.008	36
2 hr. 53 min.	0.010	36
3 hr. 43 min.	0.012	32
4 hr. 43 min.	0.019	30

In the curve taken at four minutes, the intrinsic deflection was for the first time distinctly later than in the control curves. In the subsequent curves the delay in the onset of this deflection increased until it reached approximately 0.01 second at forty-eight minutes. At seventy-five minutes, however, it was only about 0.005 second. From this time until the end of the experiment it varied between these two values. It is possible that some of these variations were due to the difficulty of placing the exploring electrode in contact with exactly the same spot at each observation. Table I gives the amplitude of the intrinsic deflection and the time of its onset with reference to the earliest ventricular deflection in standard Lead I for all the curves of the series.

Experiment III (Dog 36).—In this instance the main trunk of the anterior descending branch of the left coronary artery was ligated about one centimeter below the tip of the left auricular appendage. This operation was performed in the surgical laboratory under aseptic conditions. The small opening through which the ligation was done was immediately closed, and the chest wall was restored. No

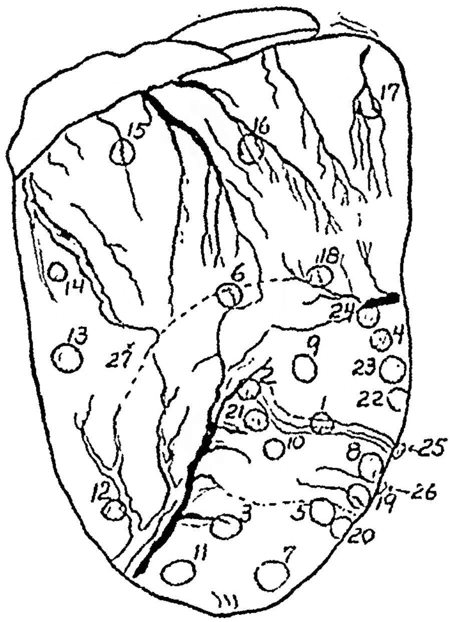

Fig. 4.—Experiment III (Dog 36). Outline drawing of the heart showing the location of the points explored by direct leads.

electrocardiograms were taken until four hours later. At this time the animal was brought to the electrocardiographic laboratory, where, after standard and precordial leads had been taken, the anterior surface of the exposed heart was explored by means of direct leads. From a number of points in the region supplied by the ligated vessel, curves were taken at intervals over a period of five and one-half hours, but all curves from the same point were found to be practically identical. The few minor exceptions appeared to be due to inaccuracy in placing the electrode on the spot it had previously occupied. We shall not need, therefore, to specify the time when each observation was made.

An outline drawing of the heart which shows the location of the points investigated is reproduced in Fig. 4, and samples of the different types of curves obtained in Fig. 5. The curves from points *3, 6, 7, 11, 12, 13, 14, 15, 16, 17,* and *18* were not obviously abnormal. It is convenient to divide the abnormal curves into two classes, but it should be noted that many of the curves obtained are transitional in form between those regarded as typical of the one class and those regarded as typical of the other.

The central portions of the infarct lay on the lateral margin of the left ventricle. In the curves from this region (points *8, 19, 20, 22, 25,* and *26*) the QRS group displays a conspicuous initial summit, and the intrinsic deflection or chief upstroke is of small amplitude. It is not possible to say with certainty whether or not the intrinsic deflection occurs slightly later than is usual in curves from the same region

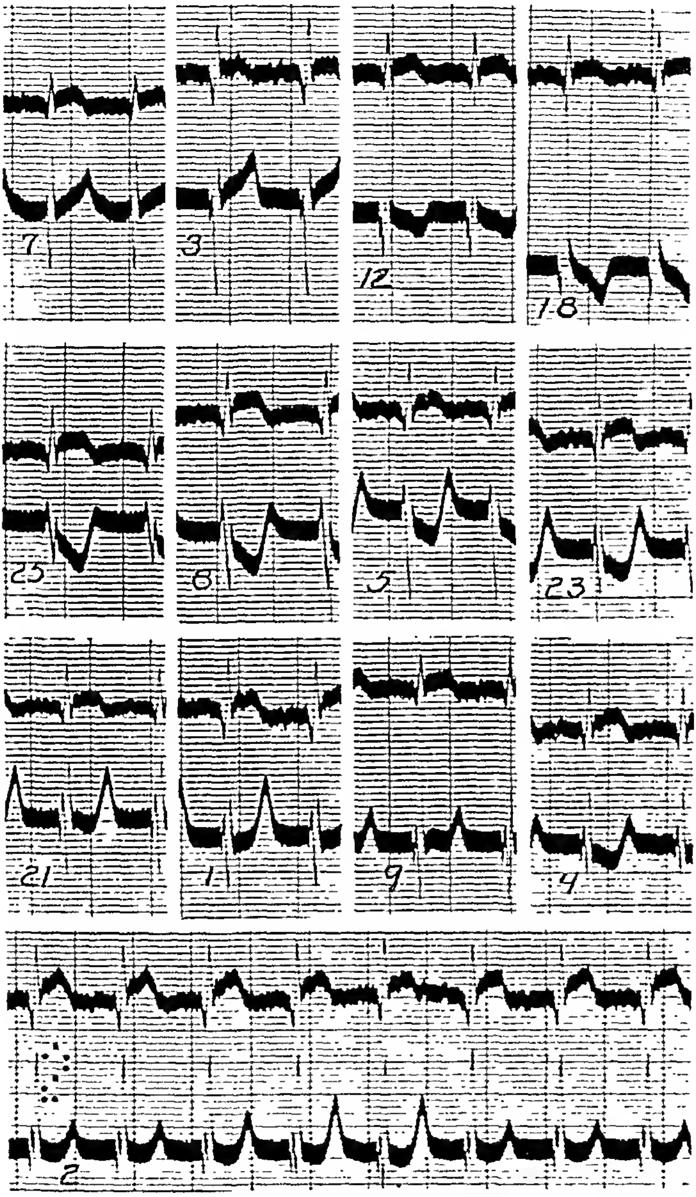

Fig. 5.—Experiment III (Dog 36). Curves obtained from various points indicated in Fig. 4.

in normal animals. The RS-T segment is displaced downward, and some of the curves show a distinct elevation at the end of the ventricular complex.

The curves from the peripheral portions of the infarct, of which that from point *21* (Fig. 5) is a characteristic example, are distinctly different in several respects. In these the QRS group shows two preliminary deflections, a sharp but small downward movement followed by a summit which corresponds in time to the initial summit

after the ligation when this lead was taken while the heart was covered with a gauze pad soaked in saline. In the second experiment the effect of covering the heart with a pad was not determined. Leads II and III were not taken in either of these experiments. In the third experiment (Dog 36) the chest wall was completely restored immediately after the artery was ligated, and no electrocardiograms were taken until four hours later. At this time the heart rate was quite slow (about 50 per minute), probably because morphine had been given. The standard leads showed no striking abnormalities as long as the chest remained intact. When the heart was exposed, however, a large Q deflection and pronounced displacement of the RS-T segment appeared in Lead I. At the same time, the heart rate rose to approximately 200 per minute.

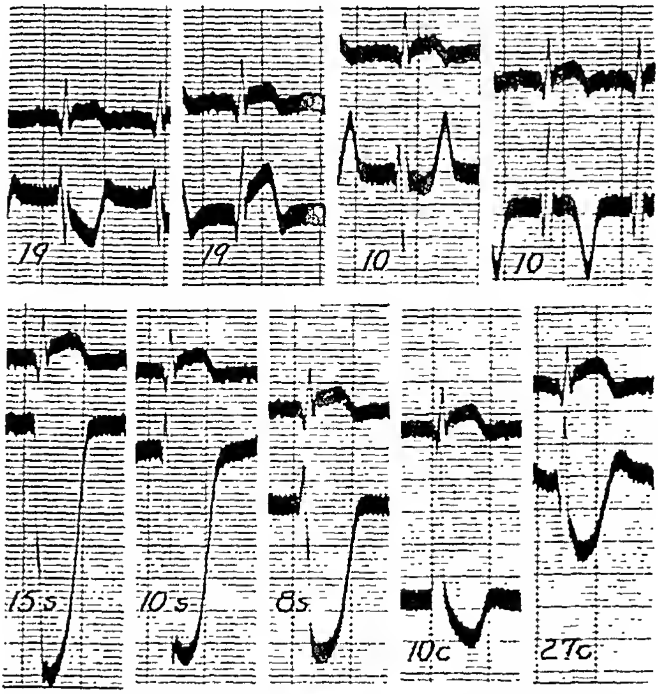

Fig. 6.—Experiment III (Dog 36). Curves obtained by leading from certain points indicated in Fig. 4. The curves of the upper row show the effect of reversing the galvanometer connections upon the form of the curves from points *19* and *10*. The curves of the lower row were taken with a sharp exploring electrode, which was pressed against the epicardial surface (*15s*, *10s*, and *8s*) or pushed through the wall into the ventricular cavity (*10c* and *27c*).

The appearance of RS-T displacement in Lead I after the heart was covered with a pad in the first experiment suggests that its absence when the heart was fully exposed was due to the lack of a satisfactory electrical contact between the anterior surface of the heart and the body tissues (see Wood and Wolferth[5]). In the third experiment, however, the RS-T displacement was absent when the chest was intact and present after the heart had been exposed, and it seems impossible that this difference can be explained by the large change in heart rate that took place when the chest was opened.

It is clear that any procedure which alters the distribution of the electrical currents produced by the heart muscle may or may not affect the form of the ventricular complex in a given lead depending upon the circumstances. Whether, in a given experiment, opening the chest and exposing the heart will diminish or accentuate the changes in the ventricular complexes of Lead I produced by ligation of the anterior descending branch of the left coronary artery would seem to depend chiefly upon the location of the infarct and of the contacts made by the heart with surrounding structures, but other factors are probably also important. After the heart was exposed in the third experiment, there was a striking resemblance between the ventricular complexes of Lead I and the inverse of the curves obtained by leading directly from the central portions of the infarct on the left margin of the heart. This resemblance was undoubtedly due to a similarity between the potential variations of the left foreleg and those at the surface of the infarct. When the chest was opened, the contact between much of those uninfarcted portions of the ventricular wall which faced toward the attachment of the left foreleg was broken, and the effect of the potential variations occurring at the epicardial surface in these regions upon the potential of this extremity was diminished or abolished. In the first experiment the infarcted region was presumably more directly anterior, and the effect of the potential variations occurring at its surface upon the potential of the left foreleg was therefore increased when the heart was covered with a pad.

In the third experiment precordial leads were taken immediately before the heart was exposed. The indifferent electrode was placed on the left leg, and the exploring electrode on the precordium, first in the midline, then over the apex beat, and finally still farther to the left. None of the resulting curves show distinct RS-T displacement. The first is certainly normal. In the last two, all the deflections are unusually small, and a distinct downward movement at the beginning of the QRS interval is absent. These curves were taken too soon after the ligation operation to preclude the possibility that some air still remained between the anterior surface of the heart and the chest wall.

Death Following Coronary Ligation.—No particular effort was expended on the study of the disturbances of rhythm that usually follow the ligation of a coronary artery, but a few observations made incidentally in the course of our experiments are worth recording. In the second experiment (Dog B) no disturbances in rhythm were observed at any time. In the first experiment (Dog A) ectopic beats of ventricular origin, represented in Lead I by complexes which vary greatly in form, were present in large numbers during the fifteen minutes immediately following the ligation. None were observed thereafter. In two other experiments (Dog C and Dog 48) in which the anterior descending

branch of the left coronary artery was ligated at a high level after the heart had been completely exposed, ventricular fibrillation occurred within less than two minutes. In one of these experiments the extrasystolic arrhythmia which preceded the onset of fibrillation was of very short duration; in the other instance it was either brief or absent. In this last experiment very pronounced alternation in the form of the ventricular complexes was observed in a direct lead from the affected area one minute after the ligature was tied (Fig. 7).

In the great majority of our experiments in which the anterior descending artery was ligated, the operation was done under aseptic conditions through a small opening in the chest wall. When the ligature was placed about the main trunk of the vessel at a high level, the immediate mor-

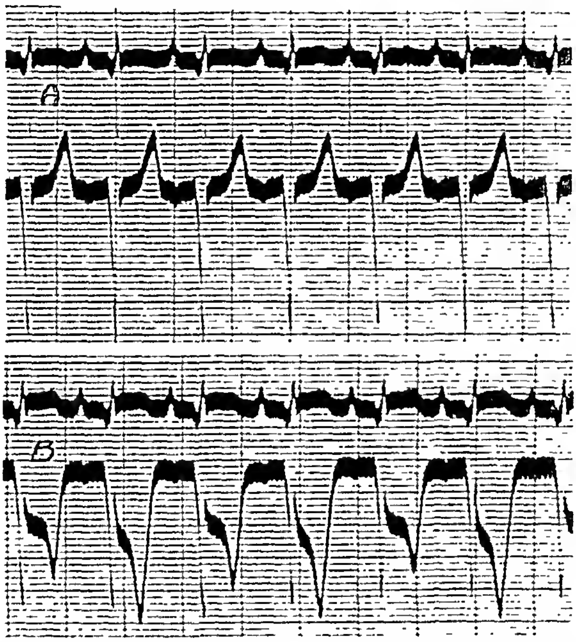

Fig. 7.—Dog C. Direct curves from a point on the left ventricle before (A) and 1 min. after (B) ligation of the anterior descending branch of the left coronary artery. In B the ventricular complex shows pronounced alternation. The heart was fully exposed when these curves were taken.

tality was very large. Seven of eighteen animals died before the chest could be restored, that is, within less than a half hour. In some instances the heart was still uncovered and under observation when it failed, and in most of these it was still contracting vigorously at the time when ventricular fibrillation developed. In others, however, the heart dilated and had practically ceased to contract before fibrillary movements began. Two animals died with symptoms of congestive cardiac failure, one thirty-six hours and the other four days after operation. One died fifteen hours after operation, probably of acute cardiac failure. Another died forty-eight hours after operation as the result of infection. Seven animals were killed after the anterior surface of the

heart had been explored by means of direct leads, and six of these were found to have large infarcts. In the other the infarct was small, probably because the ligature was not sufficiently tight to occlude the vessel completely.

In eight animals the ligature was placed around one of the larger branches of the anterior descending artery or about the main trunk of this vessel at a low level. Only one of these animals died during the operation. One died of infection four and one-half days after the ligation, and the remainder were killed after exposing the heart to obtain direct leads.

Our experience suggests that death from ventricular fibrillation is very much more likely to occur during the first half hour following ligation of a coronary artery than at a later time. It is during this period that extrasystolic disturbances appear to be most common. Ventricular fibrillation is much more often induced when the vessel ligated is a large one than when it is small. Death immediately after ligation is not always due to the onset of ventricular fibrillation; it is sometimes due to failure of the contractile mechanism without disturbances of rhythm.

DISCUSSION

The principles governing the interpretation of curves obtained by direct and semidirect leads of the kind employed in the experiments described have been adequately discussed in a previous article.[6] It was there shown that the deflections obtained by leading directly from the ventricular surface are profoundly altered when the superficial layers of the muscle beneath the exploring electrode are injured. The method used to produce the injury is immaterial. The major changes consist in a pronounced displacement of the RS-T segment and a conspicuous decrease in the amplitude of the intrinsic deflection. High grade injuries may cause this deflection to disappear. The form of the deflections which precede the onset of the intrinsic deflection is not altered. The magnitude of the changes in the RS-T segment and intrinsic deflection diminishes with the lapse of time, and they eventually disappear.

The changes induced by ligation of the artery that supplies the region with which the exploring electrode is in contact do not differ in any important respect from those that occur when this muscle is injured in some other way, and there is no reason to think that they have a different origin. Our observations indicate that certain minor differences exist but are not sufficiently extensive to prove that this is the case.

In the first experiment (Dog A) one of the changes produced by the ligation was the appearance in direct leads from the affected region of a small summit at the beginning of the QRS interval. In the second experiment (Dog B) a very thin small initial summit was present in the control curve; after the ligation this summit became distinctly larger. In the third experiment (Dog 36) a conspicuous initial summit was pres-

ent in all curves from the central part of the infarcted region. We believe that the appearance of a summit of this kind is due to a delay in the activation of the subendocardial muscle or to a decrease in the magnitude of the electrical forces which activation of this muscle produces.[6] In the first two experiments the intrinsic deflection in leads from the affected area occurred slightly later after the ligation than before, but we are not certain that the difference is significant. In two experiments (Dogs B and C) conspicuous alternation in the form of the ventricular complex of direct leads from the infarcted region occurred, and we have also called attention to the development, in such leads, of a prominent summit at the end of the ventricular complex. In the case of superficial injuries involving only the subepicardial muscle, we have not seen any of these changes, but it is unlikely that they occur only in association with the type of injury produced by destroying the blood supply to portions of the left ventricular wall.

It is hardly to be expected that the changes produced by injuring the superficial layers of muscle in a small, sharply circumscribed region will be exactly the same as those produced by ligation of an artery. The injury produced by cutting off the blood supply often involves the whole thickness of the ventricular wall and must vary greatly in degree from place to place, particularly at the margins of the affected area.

In the case of the left ventricle, infarcts old enough to have become clearly visible are as a rule more extensive on the endocardial than on the epicardial surface and frequently involve only the inner layers of muscle. It would, therefore, be most interesting to determine whether the changes in the ventricular complex produced by coronary ligation are the same in leads from the inner as in leads from the outer surface of the ventricular wall. Unfortunately, satisfactory leads from the endocardial surface are difficult to obtain. In a single experiment we determined the effect of ligating the main trunk of the anterior descending artery upon the form of the curve obtained from the cavity of the left ventricle by thrusting a sharp electrode through the wall. The curve taken before ligation was of the usual type[6] and displayed a deep U-shaped T deflection. After ligation this inverted T became somewhat smaller, but no other change occurred. The experiment was terminated prematurely by the onset of ventricular fibrillation.

Additional observations bearing upon the form of the curves obtained from the peripheral portions of left ventricular infarcts will be presented in a subsequent article. The curves from this region in the third experiment (Dog 36) differ from those obtained in other experiments in only one respect; they display a small downward movement at the beginning of the QRS interval. In all of the other curves of this class in our possession this downward movement is absent, and its significance is obscure. It is present in the curve obtained at point *10* by means of a sharp electrode (Fig. 6) and was obviously not produced by the sub-

epicardial muscle. No similar deflection occurs in the curve from the left ventricular cavity, which absence suggests that it did not depend upon the activities of muscle in distant parts of the heart but had its origin in those portions of the ventricular wall over which it was recorded. It was obtained over a large area, and a similar deflection is seen in some of the curves from points outside the infarcted region (Fig. 5). It was therefore probably present before and not produced by the ligation. Its direction indicates that the electrical forces responsible for it were produced while the excitation wave was spreading toward the exploring electrode rather than away from it. The only suggestion that we have to offer is that it may have been produced by activation of the anterior papillary muscle or of the trabeculae on the anterior endocardial surface of the left ventricular wall. Although the mechanism of its production is, therefore, not clear, its absence in other experiments indicates that it is not an essential characteristic of curves from the margins of a left ventricular infarct.

SUMMARY

The electrical activities of the heart muscle during the first few hours following ligation of the anterior descending branch of the left coronary artery were studied by means of direct and semidirect leads, taken simultaneously with standard Lead I.

During this period the principal changes in the form of the ventricular complex in direct and semidirect leads from the region whose blood supply has been destroyed consist in a pronounced displacement of the RS-T segment and a reduction in the amplitude of the intrinsic deflection or chief upstroke. Similar changes are observed in direct leads when the subepicardial muscle beneath the exploring electrode is injured in other ways.

A few hours after the ligation direct leads from the peripheral portions of the infarcted region show changes in the form of the QRS group and T deflection which are apparently characteristic and differ from those that occur in direct leads from the central portion.

Extrasystolic disturbances and ventricular fibrillation are much more likely to occur within the first half hour following ligation than later. Death during this period is not always due to the onset of ventricular fibrillation; it is sometimes due to asystole occurring without disturbances of rhythm.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION*

III.† The Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery

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The chief purpose of this article is to describe and to discuss certain changes in the form of the ventricular deflections of direct and semidirect leads produced by ligation of the anterior descending branch of the left coronary artery. The changes that occur during the first few hours immediately following ligation of this vessel have already been described,[2] and we shall confine our attention here to those observed later when the parts of the ventricular wall that have been deprived of their blood supply no longer respond to the excitatory process.

The principal methods employed in our experiments have been described previously.[1, 2, 4] Standard Lead I was taken simultaneously with all direct and semidirect leads and is represented by the upper curve in all records. The direct and semidirect leads were taken with a vacuum tube in the galvanometer circuit,[5] and the connections were so made that negativity of the exploring electrode produced an upward deflection. The distant or indifferent electrode was placed in contact with the subcutaneous tissues of the left hind leg, and the sensitivity of the galvanometer was adjusted to give a deflection of 1 cm. for 20 millivolts when taking direct and of 3 cm. for 20 millivolts when taking semidirect leads.

In taking semidirect or pad leads the exploring electrode was placed firmly in contact with a gauze pad (about 1 cm. in thickness) soaked in physiological salt solution and laid upon the exposed heart. The pad was sufficiently large to cover the heart completely and to make contact with the surrounding structures. Four curves were usually taken. In taking the first of these, the exploring electrode was placed upon that part of the pad which lay over the base of the right ventricle; with each succeeding lead it was moved 1.5 to 2.0 cm. toward the apex along a line

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†For the first two articles of this series see Wilson, Johnston, and Hill[1] and Johnston, Hill, and Wilson[2]. The observations reported in this article were briefly described in a preliminary report[3] and were also referred to in a paper read at a recent meeting of the Association of American Physicians[4].

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parallel to the long axis of the heart. The final semidirect lead was therefore from that part of the pad which lay upon the apex of the left ventricle.

In several experiments a short study of the absolute refractory period was made in order to determine whether the infarcted muscle was capable of responding normally to stimulation. For this purpose we employed the method used by Wilson and Herrmann.[6] An inductorium arranged to give single shocks was connected to a rotating device which made it possible to obtain break shocks at a constant rate. These shocks were delivered to the heart through an electrode consisting of a pair of small fishhooks, bound closely together but insulated from each other, which

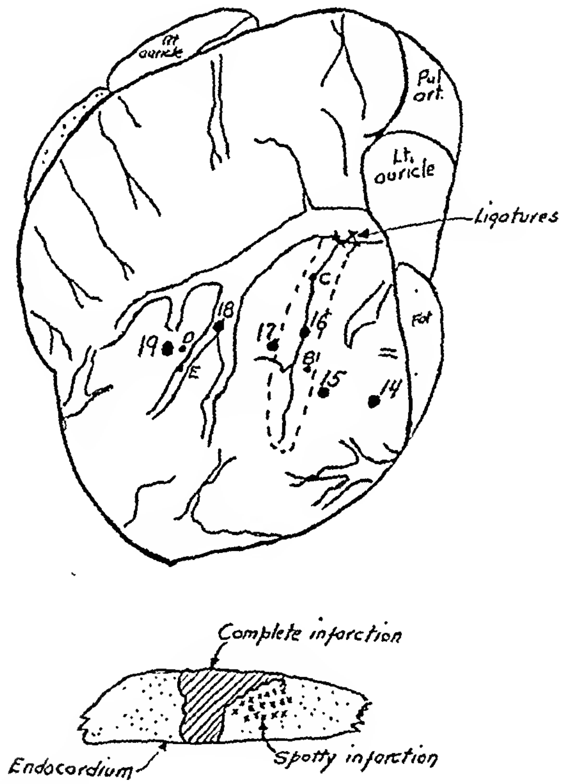

Fig. 1.—Experiment I (Dog 23). Outline drawing of the left anterolateral surface of the heart showing the location of the points from which direct leads were taken and the location of the points at which the refractory period was determined. The broken line marks the boundary of the infarcted region. Below is a sketch of a cross-section of the infarcted region about 1 cm. below the ligature.

were thrust into the superficial layers of muscle. When the rate of stimulation was adjusted so that it was only a little slower than the heart rate, each stimulus fell slightly later in the cardiac cycle than its predecessor. By measuring the time, with reference to the beginning of the QRS interval, of the latest ineffective and of the earliest effective stimulus, the approximate length of the refractory period was easily determined. The strength of the stimulus was varied by moving the secondary coil, which began to overlap the primary coil at a scale reading of approximately seven centimeters.

ILLUSTRATIVE EXPERIMENTS

Experiment I (Dog 23).—A small subdivision of the anterior descending branch of the left coronary artery was ligated. Four days later the heart was exposed, and its anterior surface was explored by means of direct leads. A series of semidirect leads was also taken. All of the semidirect and all but one of the direct curves were of the normal type. The single abnormal curve was obtained from the extreme left margin of the left ventricle. Since this region was not clearly visible, the animal was turned slightly so as to expose the left anterolateral surface of the heart. This procedure brought into view the ligated vessel and the pale zone of infarcted muscle surrounding it. Six additional direct leads were taken with the heart in this position. These curves are reproduced in Fig. 2. An outline drawing of the heart showing the location of the points from which they were obtained and the location of the infarct, and a diagrammatic sketch of a cross-section of the infarcted portion of the left ventricular wall, about 1 cm. below the ligature, are shown in Fig. 1.

Fig. 2.—Experiment I (Dog 23). The upper curve of each record is standard Lead I. The lower curves represent direct leads from the points in Fig. 1 labelled with corresponding numbers. In all direct curves a potential difference of 20 mv. is represented by a deflection of 1 cm. The connections were always so made that negativity of the exploring electrode produced an upward deflection. In all records the time interval between successive vertical lines is one-fifth second.

The curves from points *14, 18,* and *19* do not differ in any important respect from those usually obtained from the corresponding portions of the normal heart. The curves from points *16* and *17*, both of which lay within the boundaries of the infarcted region, are of an entirely different kind. In these curves the QRS group consists of a single tall summit, and there is no trace of a true intrinsic deflection. There is, in other words, no sudden upstroke, represented by a thin and barely visible line as in the curves from points *18* and *19*, which can be ascribed to the arrival of the excitatory process beneath the exploring electrode. The T-wave is represented by a U-shaped depression followed by a small elevation. These ventricular complexes closely resemble those obtained when the exploring electrode is thrust through the heart wall into the cavity of the left ventricle.[7]

In the curve from point *15*, which was near the margin of the infarct, the QRS group begins with an abnormally large upward movement and the intrinsic deflection is of unusually small amplitude. In our experiments curves of this type were most often obtained from regions where only the inner layers of the ventricular wall were infarcted.

The refractory period was tested at the four points labelled *B*, *C*, *D*, and *E* in Fig. 1. The last two points lay close together on healthy muscle. The first point, *B*, was very close to the margin of the infarct and the second, *C*, was well within its boundaries. The time of the latest ineffective and that of the earliest effective stimulus at each point are given in Table I. It will be seen that the healthy muscle yielded definitely lower figures than the infarcted muscle. The figures for point *C* vary with different tests, possibly because the position of the stimulating electrode varied slightly with different applications. Such minor discrepancies are common in experiments of this kind, and their cause is not easily determined.

TABLE I.*

REFRACTORY PERIOD IN EXPERIMENT I (DOG 23)

POINT	CURVE NO.	COIL AT	HEART RATE	LATEST INEFFECTIVE STIMULUS	EARLIEST EFFECTIVE STIMULUS
D	990	6 cm.	192-193	0.148	0.153
E	993	6 cm.	186-188	0.155	0.157
B	988	6 cm.	195-198	0.177	0.181
C	989	6 cm.	195	0.204	0.209
C	991	6 cm.	188	0.198	0.202
C	992	6 cm.	187-188	0.177	0.180

*The secondary coil began to overlap the primary at a scale reading of approximately 7 cm. In this experiment the healthy muscle began to respond with the secondary coil at 12 cm. The infarcted muscle did not begin to respond until it was moved up to between 8 and 9 cm. The curve numbers are given to indicate the order in which the different tests were made. The measurements given in this and later tables were made for us by Dr. John Nyboer.

Experiment II (Dog 19).—In this instance the electrocardiographic study was made forty-eight hours after ligation of the main trunk of the anterior descending branch of the left coronary artery. The first curves taken showed long periods of idioventricular rhythm separated by very short periods of normal sinus rhythm. The idioventricular rate was approximately 190 per minute and only a little faster than the sinus rate. When the vagi were cut the sinus rate rose to approximately 240 per minute, and the abnormal rhythm was abolished. An idioventricular rhythm of this type was observed in many of our experiments. It was probably induced in part by the administration of morphine, which in the dog enhances vagal tone and promotes ventricular escape, and in part by effects produced by coronary ligation. In those experiments in which there was no myocardial infarction it was not observed.

The infarct was a very extensive one; it involved the greater part of the anterior surface of the left ventricle. On opening the chest it was noted that the affected region was paler in color and showed less contractile movement than the rest of the heart wall. A photograph of the inner surface of the left ventricle is reproduced in Fig. 3; it shows a large area of pale muscle largely covered by subendocardial hemorrhage. On the cut surface the pale muscle extended completely through the ventricular wall. The septum was not grossly involved, but close to its anterior attachment on the endocardial surface of the right ventricular wall a few islands of infarcted muscle were visible.

An outline drawing of the anterior surface of the heart showing the location of the infarct and of the points from which direct leads were taken is reproduced in Fig. 4, and samples of the curves obtained are shown in Fig. 5. The curves from points *6, 7, 11, 12, 13, 14, 17, 18,* and *21* are not abnormal; in all of these the QRS group begins with a conspicuous downstroke and the intrinsic deflection is of large amplitude. The curves from points *1, 2, 3, 4, 5, 8, 9, 10, 15, 16, 19,* and *22,* which were on the infarcted portion of the heart wall, are similar in general outline to those obtained from the infarcted region in Experiment I. The first and only prominent deflection of the QRS group is upward, and T is definitely inverted in all but one instance. Many of these curves, however, differ from the corresponding curves of Experiment I in one respect. The QRS group displays a small but sharp upstroke, which apparently represents the intrinsic deflection greatly reduced in

Fig. 3.—(Dog 19.) Photograph of the endocardial surface of the left ventricle. A pin at the right margin of the infarct marks the attachment of the septum to the anterior ventricular wall.

amplitude. In some instances this upstroke gives rise to a conspicuous notch on the descending limb of the initial summit (Fig. 5, Curves *2* and *8*); in others it occurs at the end of this deflection and begins below the baseline (Fig. 5, Curves *1* and *5*). The curve from point *20,* unlike the other curves from the infarcted region, shows a very small initial downward movement.

A set of four semidirect or pad leads was also taken. In the first of the curves so obtained the QRS group begins with a large downward movement; in the second the initial downward movement is small; in the last two it is absent and the ventricular complexes resemble those obtained by direct leads from the surface of the infarct. In standard Lead I the most prominent deflection of the QRS group is a large initial downward movement, or Q-wave. Before the vagi were cut the T

deflection was sharply inverted (Fig. 5, Curves *1 and 14*), but afterward the inversion was less pronounced. In Lead III the first and most prominent deflection of the QRS group was upward, and T was a pointed summit.*

The location of the points at which the refractory period was tested is shown in Fig. 4, and the measurements of the corresponding curves are given in Table II. These points have been divided into three groups. At the points of the first group (points *K, L, D, B,* and *H*) the duration of the refractory period was about 0.14 ± 0.02 second. At the points of the second group (points *E, F, Q, O,* and *N*) it was somewhat greater. At three of the four points (*A, G, M,* and *P*) of the third group no responses could be elicited; at the fourth point, *A*, the length of the refractory period varied with different tests, possibly because the stimulating electrode was not accurately replaced.

TABLE II

REFRACTORY PERIOD IN EXPERIMENT II (DOG 19)

POINT	CURVE NO.	COIL AT	HEART RATE	LATEST INEFFECTIVE STIMULUS	EARLIEST EFFECTIVE STIMULUS
K	947-3	6.75 cm.	240-244	0.121	0.130
L	948-1	6.75 cm.	231-238	0.117	0.133
L	949-1	6.75 cm.	232-236	0.131	0.151
D	945-1	6.75 cm.	238	0.123	0.134
D	951-1	6.75 cm.	231	0.134	0.141
D	952-2	6.75 cm.	229-231	0.132	0.145
B	943-2	8.25 cm.	244-245	0.126	0.169
H	947-2	6.75 cm.	238-240	0.128	0.164
E	946-1	6.75 cm.	240	0.144	0.182
Q	952-1	6.75 cm.	228-232	0.174	0.175
F	946-2	6.75 cm.	240	0.166	0.177
O	950-2	6.75 cm.	226-234	0.178	0.190
N	950-1	6.75 cm.	234-240	0.185	0.188
A	943-1	8.25 cm.	242-244	0.173	0.197
A	944-1	6.75 cm.	242	0.209	No responses
A	945-2	6.75 cm.	242-244	0.185	0.208
G	947-1	6.75 cm.	239-240	0.243	No responses
M	949-2	6.75 cm.	230	0.243	No responses
P	951-2	6.75 cm.	230	0.255	No responses

Experiment III (Dog 29).—The electrocardiographic studies were made four days after ligation of the anterior descending branch of the left coronary artery. Before the chest was opened for the purpose of taking direct leads, the standard limb leads and a set of three precordial leads were taken. In taking the precordial leads, the indifferent electrode was placed on the left hind leg; the exploring electrode consisted of a copper disk about one inch in diameter which was sewn under the skin of the precordium. For the first precordial lead this electrode was placed in the midline at the midprecordial level; for the second, directly over the apex beat; and for the third, about seven centimeters to the left of the apex beat. In all three precordial curves the prominent downstroke with which the QRS group of the precordial electrocardiograms of normal animals ordinarily begins was absent; the ventricular complexes were similar to those obtained later by leading directly from the surface of the infarcted region. The ventricular complexes of the standard leads were similar to the curves of the Q_1 T_1 type frequently obtained in cases of

*Standard Leads I and III of this animal (Dog 19) were reproduced in the first article of this series.[1] See Fig. 7*E* of that article. The standard curves of Dog 29 (Experiment III) are shown in Fig. 7*J* of the same article. In all the articles of this series the same numbers are employed in referring to the animals used in our experiments.

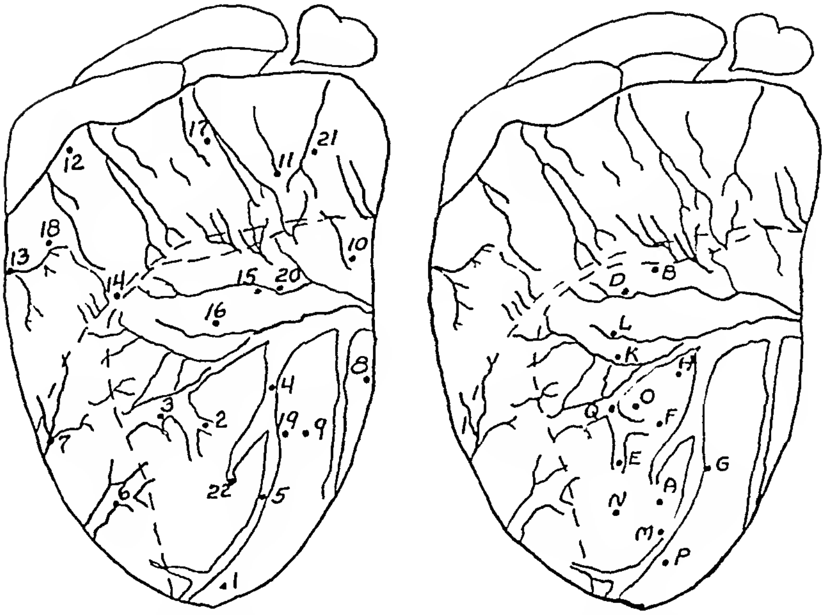

Fig. 4.—Experiment II (Dog 19). Outline drawings of the anterior surface of the heart showing the location of the points from which direct leads were taken (on the left), and of the points at which the refractory period was determined (on the right).

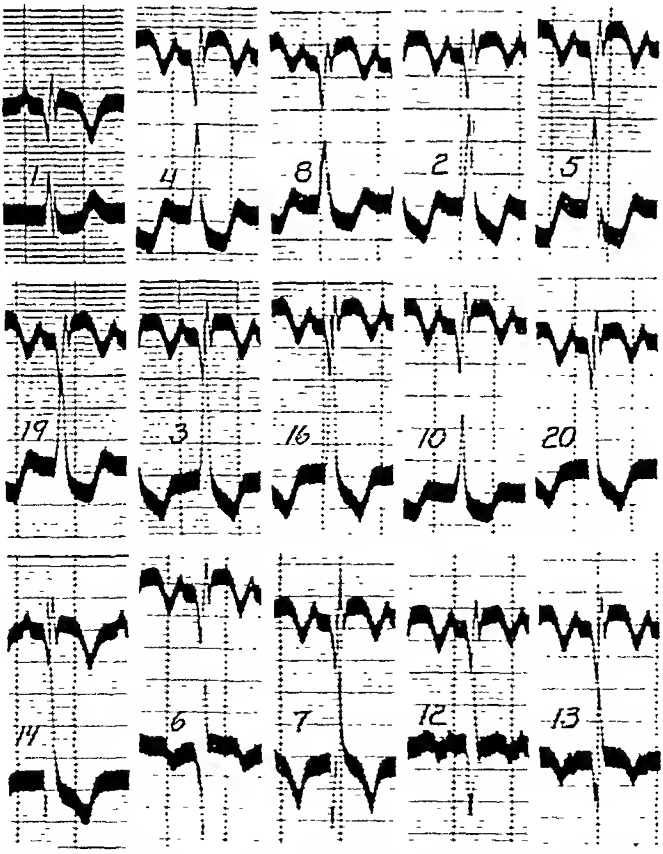

Fig. 5.—Experiment II (Dog 19). Direct leads from the points in Fig. 4, which bear the corresponding numbers. The upper curve of each record is standard Lead I. The curves numbered *1* and *14* were taken before, the remainder after cutting the vagi.

infarction of the anterior wall of the human heart;[8] there was a very large Q deflection in Lead I and a small R and deep S in Lead III.

When the heart was exposed, it was observed that a large part of the anterior wall was abnormally pale, relatively immobile, and usually firm in consistence. It was subsequently found that the lower third of the posterior wall showed similar changes. When the heart was opened, the involvement on the inner surface of the left ventricle was seen to correspond in distribution to the involvement of the outer surface. On the endocardial surface of the free wall of the right ventricle a few small areas of infarction were found near the attachment of the septum; the septum itself did not appear to be involved.

The approximate boundaries of the infarcted region and the location of the points explored are shown in Fig. 6. The curves from points *7, 8, 9, 10, 11,* and *17,* which were outside the affected region, were of the normal type; in these the QRS group showed a characteristic intrinsic deflection preceded by a conspicuous downward movement (Fig. 7). The curves from points *1, 2, 3, 4, 5, 6, 12, 13, 14, 15, 16, 18,* and *19,* all within the boundaries of the infarct, were of the same type as those ob-

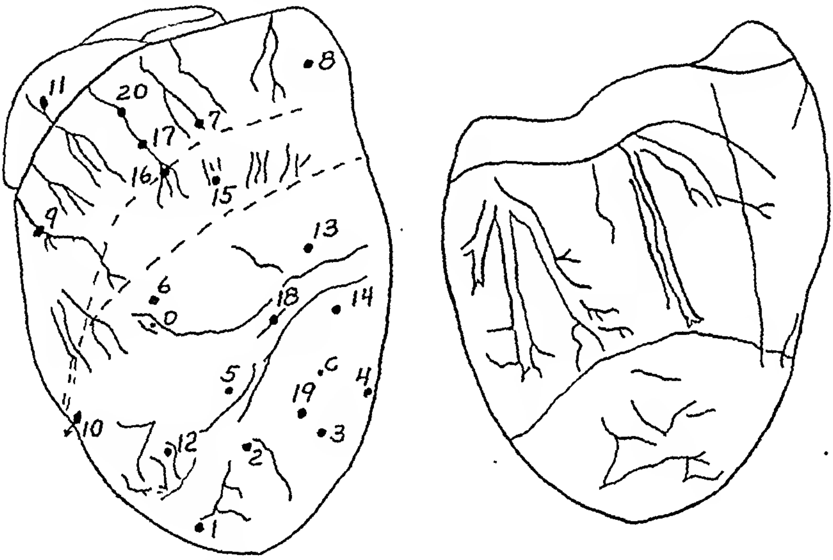

Fig. 6.—Experiment III (Dog 29). Outline drawings of the anterior (on the left) and posterior (on the right) surfaces of the heart showing the location of the points from which direct leads were taken and the location of the points at which the refractory period was determined. The upper broken line in the drawing on the left marks the upper boundary of the infarct; the lower broken line marks (approximately) the anterior attachment of the ventricular septum. In the drawing on the right the upper boundary of the infarct is marked by a solid line.

tained from the infarcted region in the experiments already described. They displayed no true intrinsic deflection and no conspicuous downward movement during the QRS interval; the sole deflection of the QRS group was upward.*

Instead of testing the refractory period at a large number of points as in Experiment II, only three points were stimulated, but the strength of the stimulus was varied through a wide range. One of the points investigated (point *C* near point *19*) was near the apex and in the central part of the infarcted region. The second point (point *D* near point *6*) was close to its margin, and the third (point *7*) was just outside its boundary. The figures which define the refractory period at these three points for stimuli of various strengths are given in Table III. In the case of point *7* a great increase in the strength of the stimulus had no appreciable effect upon the duration of the refractory period. At point *D* the refractory period was

*Some of the complexes of the curve from point *16* showed a small initial downward movement; in other complexes this deflection was absent.

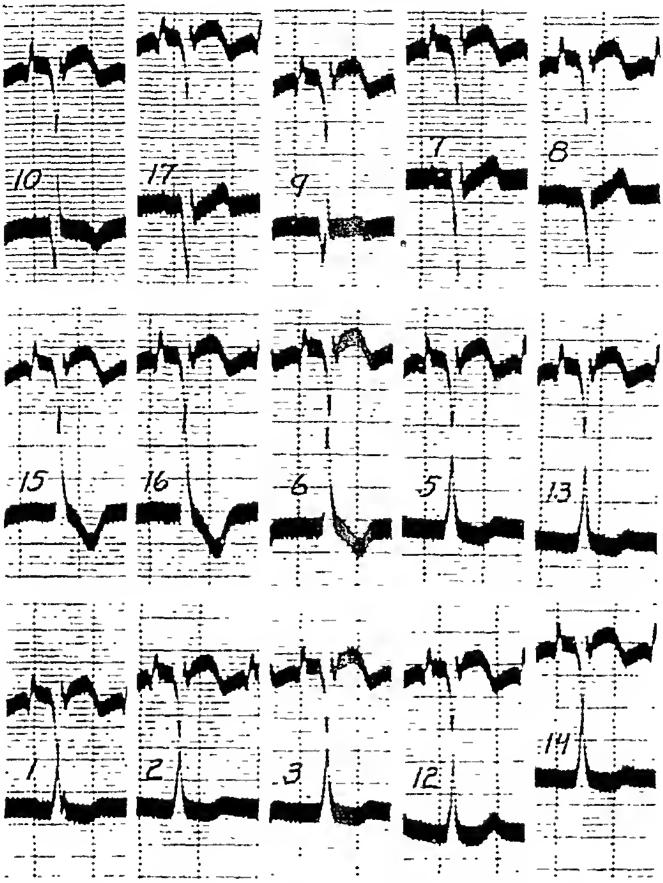

Fig. 7.—Experiment III (Dog 29). Direct leads from the points in Fig. 6, which bear corresponding numbers. The upper curve of each record is standard Lead I.

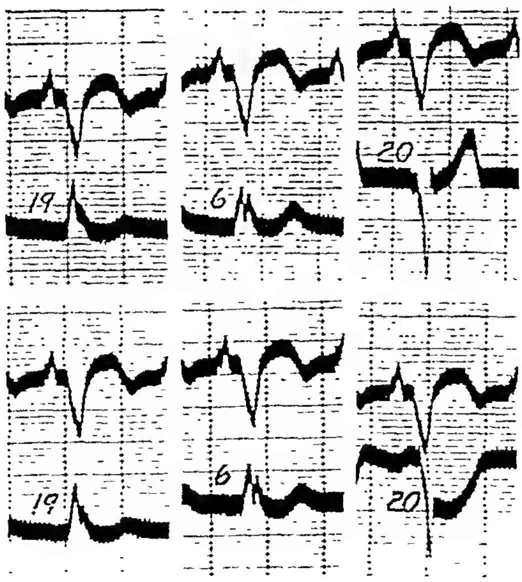

Fig. 8.—The lower curves represent direct leads taken before (upper row) and after (lower row) burning the muscle beneath the exploring electrode. The upper curve of each record represents standard Lead I. These curves were taken after the right branch of the His bundle had been cut. The direct curves were obtained by leading from the points in Fig. 6, which bear corresponding numbers.

definitely longer than at point *7* for stimuli of all strengths. The figures obtained are not entirely consistent, but apparently there was a tendency for the refractory period to shorten as the strength of the stimulus was increased. At point *C* only the strongest stimuli produced responses, and the period during which the muscle was refractory even to these was very long.

Table III

Refractory Period in Experiment III (Dog 29)

POINT	CURVE NO.	COIL AT	HEART RATE	LATEST INEFFECTIVE STIMULUS	EARLIEST EFFECTIVE STIMULUS
7	R11	8 cm.	167	0.146	0.169
7	R14	8 cm.	158-160	0.183	0.185
7	R20	6 cm.	154	0.148	0.177
7	R19	4 cm.	153-155	0.159	0.170
7	R27	1 cm.	147	0.161	0.172
7	R28	1 cm.	148	0.058	0.176
D	R13	8 cm.	161-162	0.218	0.223
D	R17	8 cm.	158	0.249	0.258
D	R24	6 cm.	152-153	0.201	0.219
D	R18	5 cm.	158-159	0.201	0.210
D	R23	4 cm.	152-153	0.199	0.200
D	R25	1 cm.	146-148	0.195	0.212
C	R15	8 cm.	160	0.364	No responses
C	R21	6 cm.	155	0.295	No responses
C	R16	5 cm.	158	0.336	No responses
C	R22	4 cm.	152	0.289	0.332
C	R26	1 cm.	146	0.287	0.300

After the right branch of the His bundle had been cut in order to determine the effect of the infarct upon the form of the levocardiogram,[1] it was decided to adopt a different method of studying the condition of the muscle at or near the three points where the refractory period had been measured. Direct leads were taken from points *19*, *6*, and *20* immediately before and again immediately after the superficial layers of muscle surrounding each of them had been burned with a hot iron. At point *20* the injury resulted in pronounced downward displacement of the S-T segment and a conspicuous reduction in the amplitude of the intrinsic deflection (Fig. 8); at points *6* and *19* it produced no change whatsoever in the form of the ventricular complex (Fig. 8). It may be concluded that the muscle at point *20* was living but that the superficial muscle at points *6* and *19* was dead, or at least incapable of responding to the natural excitatory process. It is therefore probable that stimulation at these last two points produced responses only when the strength of the stimulus was increased to a point where a current of stimulating value flowed in the nearest muscle that was still living.

COMMENTS

We have recently discussed[7] in some detail the principles that govern the interpretation of the galvanometric curves obtained by epicardial and semidirect leads of the kind employed in the experiments described in this article. It has been pointed out that the conspicuous downstroke which immediately precedes the intrinsic deflection in direct leads from the epicardial surface of the normal ventricular wall represents the spread of the excitatory process from within outward through that portion of the wall subjacent to the exploring electrode. The polarity

of these electric forces is such as to make the epicardial surface positive with respect to the endocardial surface and to points distant from the heart. The intrinsic deflection itself represents the sudden change in the potential of the exploring electrode which occurs when the arrival of the excitatory process at the epicardial surface brings these forces, and hence the electromotive force across the ventricular wall, to an end, and thus allows the exploring electrode to assume the potential of the adjacent portions of the ventricular cavity. When the ventricular wall beneath the exploring electrode is dead, it does not respond to the excitatory process, and the endocardial and epicardial surfaces undergo similar variations in potential. The curves obtained from the epicardial surface then resemble those obtained from the adjacent portions of the ventricular cavity; there is no conspicuous downward movement during the QRS interval, and no true intrinsic deflection occurs.

According to this view, the large initial summit of the QRS group in direct leads from infarcted portions of the ventricular wall represents potential variations practically identical with those that take place in the ventricular cavity and is due to the suppression of the electrical forces normally produced by the outward spread of the excitation process through that part of the ventricular wall with which the exploring electrode is in contact. When this deflection is the sole deflection of the QRS group and is unnotched, it is assumed that all the muscle lying between the exploring electrode and the ventricular cavity is dead, or at least that it no longer responds to the natural stimulus. When this deflection displays a conspicuous notch ending in a sharp upstroke, as in some of the curves obtained in Experiment II (Dog 19), it is assumed that some of this muscle is still responding, but whether a small amount of muscle is producing electrical forces of normal magnitude or a large amount of muscle is producing electrical forces of subnormal magnitude is not easily determined. It is clear that even normal muscle will not respond unless there is some route by way of which the excitatory process can reach it; in cases of the kind under consideration we cannot, therefore, suppose that we are dealing with islands of healthy tissue completely surrounded by dead tissue. We may, however, be dealing with the converse, islands of dead tissne separated by layers of living muscle. It should be noted that the duration of the QRS group in leads from the infarcted region is not obviously increased, and, if any muscle in this region responded, the delay experienced by the excitation wave in reaching it must have been relatively slight. In all of our experiments there was an exact correspondence between the region which yielded abnormal curves of the kind described and the region which showed gross signs of infarction. There is no reason to suspect that the abnormalities noted were in any way dependent upon involvement of the branches of the His bundle, of their major subdivisions, or even of the Purkinje plexus.

They were apparently due directly to the infarction of the ordinary muscle of the ventricular wall and the resulting disappearance of the electrical forces normally produced by the muscle affected.

In most of our experiments the RS-T segment and the T deflection of the curves from the infarcted region were represented by a U-shaped depression, sometimes followed by a small summit. In some instances, however, there was no definite displacement of the RS-T segment, and T was frankly upright. Curves from the left ventricular cavity usually display final deflections of the former kind.

It was our hope that studies of the refractory period of the infarcted region would yield important information regarding the ability of the affected muscle to respond to the excitatory process. It soon became apparent, however, that such studies had very little if any value. It is obvious that, if the strength of the stimulus is sufficiently increased, the current flowing will rise above threshold value even in those parts of the heart most distant from the stimulating electrode. If several points on the surface of the infarcted region are found to differ as regards the apparent duration of the refractory period, or with respect to the strength of the stimulus required to produce a response, the differences found may depend either upon differences in the condition of the muscle at these points, or merely upon variations in the distance of the point stimulated from healthy muscle. It is probable that the reduction in the length of the refractory period observed in our experiments when the stimulating electrode was moved from the central toward the peripheral portions of the infarcted region has no significance. This is certainly true in the case of Experiment III, in which the form of the ventricular complexes obtained by leading directly from the two points in the infarcted region at or near which the refractory period was determined was not altered by burning the muscle upon which the exploring electrode rested.

In the experiments in which ligation of the anterior descending branch of the left coronary artery produced a very large infarct, the QRS group of standard Lead I began with a large downstroke, or Q deflection. It is perhaps worth noting that the apex of this deflection and that of the initial summit of the curves obtained by leading from the central portions of the infarct were always nearly simultaneous. This relation suggests that the large Q deflection and the initial summit of the direct leads have a similar origin.

SUMMARY

One to four days after ligation of the anterior descending branch of the left coronary artery or one of its subdivisions, the anterior surface of the dog's heart was explored by means of direct and semidirect leads. In taking these leads, the exploring electrode was paired with an in-

different electrode placed on the left hind leg, and the connections were so made that relative negativity of the former electrode produced an upward deflection in the completed record.

The curves obtained under these circumstances by leading directly from the epicardial surface of the infarcted region have a characteristic outline. The initial and usually the sole deflection of the QRS group is a tall summit. The downward movement which normally precedes the intrinsic deflection in direct leads from the ventricular surface is absent. The intrinsic deflection is likewise absent, or is greatly reduced in amplitude in which case it is often represented by a deep notch on the descending limb of the initial upward deflection. The RS-T segment and T-wave are usually represented by a U-shaped depression, sometimes followed by a small summit.

Curves of similar form are obtained when the exploring electrode is separated from the epicardial surface by a pad of gauze soaked in physiological salt solution or by the precordial tissues of the intact chest wall.

The curves in question are very much like those obtained by introducing the exploring electrode into the cavity of the left ventricle. They owe their characteristic form to the absence of the electrical forces normally produced by the portion of the ventricular wall deprived of its blood supply.

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THE CEREBRAL BLOOD FLOW IN MAN AS INFLUENCED BY ADRENALIN, CAFFEIN, AMYL NITRITE AND HISTAMINE*

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ALTHOUGH there is a considerable literature dealing with the action of various drugs on the blood supply to the brain, most of it is based upon experiments conducted on animals under an anesthetic. Observations on man have been indirect and, for the most part, fragmentary. Changes in spinal fluid pressure, or in the tension of oxygen in the internal jugular vein, have given presumptive evidence of alterations in blood flow, and studies on the changes in caliber of the cerebral blood vessels at operation have yielded interesting data. Much more questionable are deductions derived from observations of the action of drugs on systemic blood pressure or on the circulation in the skin and other organs of the body, for previous studies from this laboratory have shown that the cerebral circulatory response to either nervous or chemical stimuli may be the opposite of the response of blood vessels elsewhere in the body.[1]

The effect on the cerebral circulation of numerous important drugs has not been investigated, and among those that have, a confusion of testimony exists. Results of animal experimentation are often not applicable to clinical problems. The securing of accurate information from human subjects is of extreme importance, because of its bearing on the treatment of those conditions in which the blood supply to the brain is endangered. The chief clinical interest lies in knowing the effect of a drug on the volume of blood flowing through the brain, for a defective supply of blood and of oxygen quickly interferes with cerebral activity.

MATERIAL AND METHODS

The device which we have used for registering changes in blood flow is a thermoelectric flow recorder previously described by one of us.[2] It consists essentially of a fine wire stilet with an electrically heated tip. This stilet is thrust through a hollow needle into the lumen of the internal jugular vein. A constant electric current is applied to the tip of the stilet, sufficient to heat it to a temperature a degree or two

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above that of the blood. As the blood flows past the heated tip of the stilet, the tip is cooled. The faster the blood flows, the cooler the tip becomes; the slower the blood flows, the hotter the tip becomes. The temperature of the tip is measured by means of thermojunctions in series with a galvanometer. In order that a change in body temperature should not be misinterpreted as a change in flow, the cold junction is mounted on the stilet behind the hot junction; it then becomes possible to measure not the absolute temperature of the tip, but the difference in temperature between the heated tip and the body of the stilet. This difference in temperature varies only slightly with changes in body temperature but greatly with changes in blood flow.

The instrument records changes in the velocity of the surrounding stream. If, however, the cross-section area of the stream remains constant, changes in velocity may be interpreted as changes in volume flow. The tip of the stilet in our experiments was in the internal jugular vein close to its point of exit from the skull, a situation where only slight changes in the caliber of the vessel could occur, for where the vessel pierces the skull, it has essentially rigid walls. We believe, therefore, that we are warranted in interpreting changes in velocity as being due to changes in volume flow.

The data obtained are only roughly quantitative. They furnish no absolute values for volume flow; they indicate only the direction and general magnitude of alterations in volume flow. Because it is impossible to duplicate exactly the position of the stilet in the vein, records from separate experiments are only roughly comparable, as regards the magnitude of the changes. They are, however, strictly comparable as regards the direction of these changes. Respiratory movements and blood pressure were recorded simultaneously with cerebral blood flow.

This study was conducted on patients in the Neurological Unit of the Boston City Hospital, most of whom were subject to epileptic seizures. In each case, the subject gave his full consent to the procedure carried out.

EPINEPHRINE

Well known is the fact that adrenalin acts in general as a vasoconstrictor and produces pallor of the skin. Concerning affairs inside the cranium, the testimony in the literature has been somewhat confusing; only the most recent animal experimental work need be quoted. The primary action of adrenalin on pial arterioles, as on those elsewhere, is one of constriction. This is shown by local application to the pia mater (Forbes, Finley and Nason[3]) and by the experiments of Finesinger and Putnam[4] in which with the pressure of the perfused

blood maintained at a constant level, injected epinephrine caused a 44 per cent decrease in the volume of blood flowing through the head, and a 10 per cent decrease in the diameter of pial arteries. When, however, the increase of blood pressure was unrestricted, intracarotid injection of epinephrine caused a 13 per cent dilatation of pial vessels, and simultaneously an 85 per cent constriction of the vessels of the animal's ear.[3] These experiments indicate that a rise in blood pressure can overcome epinephrine vasoconstriction within the head but not outside. They suggest that the drug increases the cerebral circulation. With an instrument of the same general type as that used here, Schmidt and Pierson[5] have found that epinephrine injected intravenously produces an increased blood flow through the medulla of cats.

In eleven instances we injected a solution of epinephrine chloride intravenously. The results were unequivocal. In every case, there was an abrupt and great acceleration of blood flow. In eight instances, the amount injected, from 0.1 to 0.2 c.c. of a 1/1,000 solution, was sufficient to cause a sharp increase in blood pressure and in pulse rate. The curves representing blood flow and blood pressure were so similar in form that it seems evident that the increase in flow was in the main secondary to the increase in systemic blood pressure.

One of the records obtained is produced in Fig. 1. Following the injection of 0.1 c.c. of a 1/1,000 solution of epinephrine, there was a marked and sudden increase in blood flow. The fact that the blood flow curve is flatter at the top than the curve of blood pressure is possibly due to the characteristics of the flow recorder, for it has a "ceiling" beyond which pronounced increases in flow do not register correspondingly great changes in temperature.

The amount of epinephrine which we injected in our first experiments was undoubtedly greater than the amount secreted into the blood stream by the adrenals, and, therefore, the experiments do not represent physiological conditions. On three occasions we used much smaller doses, from 0.01 to 0.005 of a 1/1,000 solution. In each instance there was a moderate increase in flow without, however, a corresponding and simultaneous increase in blood pressure. The latter either fell or remained constant. The heart rate increased. Our evidence, therefore, indicates that in man the intravenous injection of adrenalin in amounts too small to raise blood pressure, as well as in larger nonphysiological dosage, produces an increase in cerebral blood flow.

CAFFEIN

Because clinicians have found that caffein is valuable for patients having the Cheyne-Stokes type of respiration, it has been assumed that

caffein acted to improve the cerebral and especially the medullary circulation. The experimental work with caffein has, however, been confusing.

Finesinger[6] has reviewed the literature. His own study showed that the response of the pial vessels in cats differed with the type and extent of the anesthesia and with the initial blood pressure. When the animal had recovered from ether, caffein injected intravenously caused the pial artery to constrict momentarily and then to dilate. In human subjects, Stevenson and his coworkers,[7] using a tambour covering a skull defect, obtained a drop in intracranial pressure, and Loman and Myerson,[8] a fall in spinal fluid pressure with no change in internal jugular venous

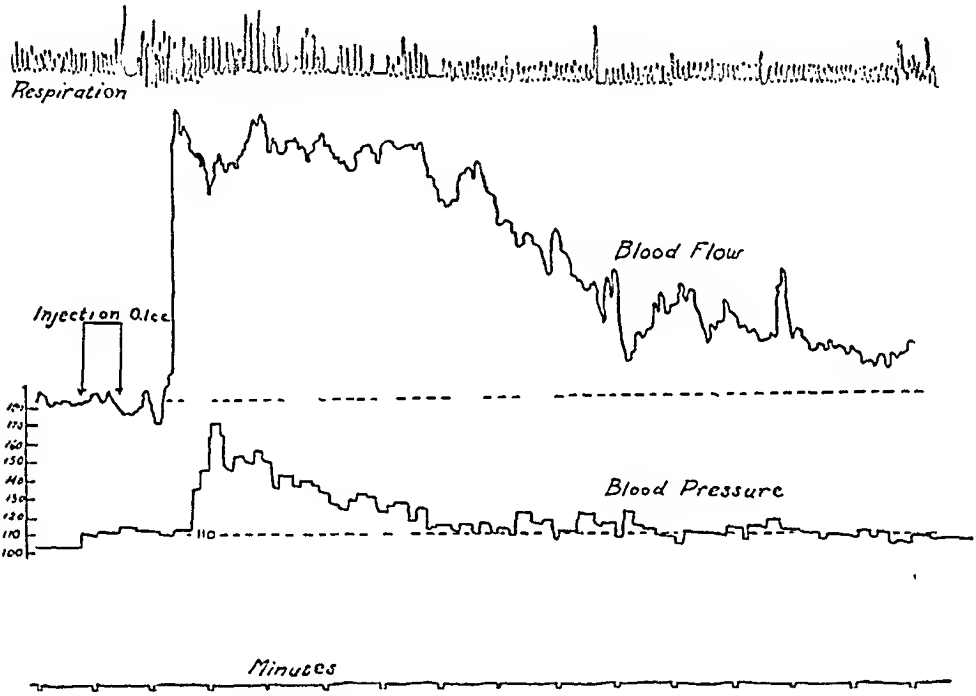

Fig. 1.—Effect of large dose of adrenalin on cerebral blood flow.

The tracing labeled "blood flow" is a record of the blood flow through an internal jugular vein. Above this is a record of chest movements. Below is a record of systolic blood pressures taken by the auscultatory method with the cuff on the upper arm. The maximum increase from the level at the time of injection was 60 mm. The bottom record gives time in minutes. The arrows indicate the period of injection.

pressure. These authors conclude that caffein causes a decrease in brain volume. However, such a fall in intracranial pressure could be caused by vasoconstriction due to a lowered blood CO_2 resulting from a caffein-induced hyperpnea.[1] Finesinger and Putnam,[4] using monkeys and keeping blood pressure constant, found that caffein caused an increase in cerebral flow of 116 per cent. There is no experimental evidence in the human subject to show whether the net result of the action of caffein on blood vessels, on respiration, and on blood pressure produces an increase or a decrease in cerebral blood flow.

Six experiments were conducted in which 0.5 gm. caffein sodium benzoate was injected intravenously. In five of the tests, within a minute, there was a gradual fall in flow. In all but two instances, after from two to ten minutes of diminished flow, it again increased to or slightly above its preinjection level (Fig. 2). Of particular importance in these observations is the fact that in all the cases the caffein caused a slight elevation of blood pressure.

A decrease in cerebral blood flow in the face of an increased blood pressure must mean that a cerebral vasoconstriction occurred due, per-

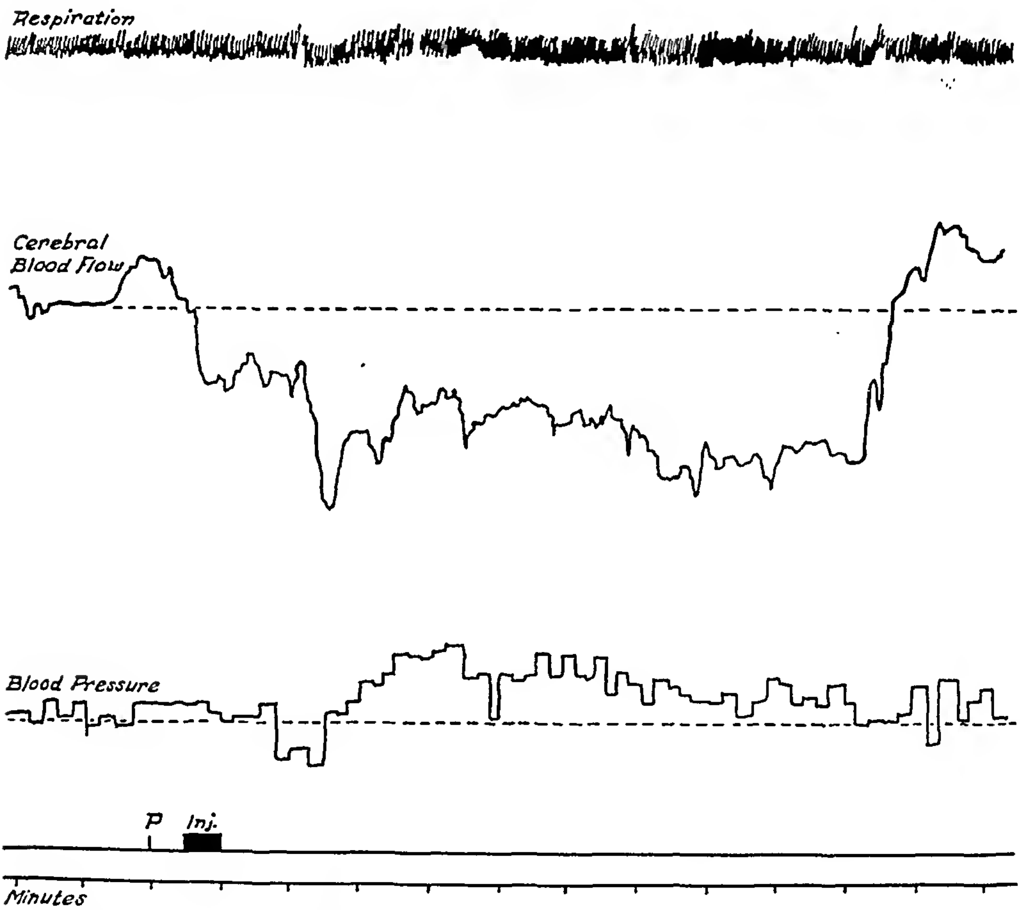

Fig. 2.—Effect of caffein on cerebral blood flow.

The curves have the significance as in Fig. 1. At *P* the needle was inserted into an arm vein. During period marked "Inj.," 0.5 gm. of caffein sodium benzoate was injected into blood stream. The maximum increase in blood pressure from the preinjection level was 33 mm. Hg.

haps, to the alkalosis induced by the stimulation of respiration. These findings are not in full accord with the experimental results in animals referred to above, but they are in accord with the indirect evidence on man obtained by other authors.

The beneficial effects of caffein in Cheyne-Stokes breathing cannot be explained by an improved circulation, unless it is assumed that increased flow occurs in only a certain small portion of the brain. If

circulation alone were responsible for clinical improvement from the use of caffein, yet greater benefit would be anticipated (but does not occur) from epinephrine.

AMYL NITRITE

The flushing of the skin and sharp drop in blood pressure which follow inhalation of amyl nitrite indicate a profound dilatation of arterioles. That this occurs also in cerebral vessels is proved by the throbbing sensation in the head, by the prompt rise in spinal fluid pressure of humans, and by the observed dilatation of pial arterioles of cats.[9] In the presence of both a dilatation of arterioles and a fall in systemic

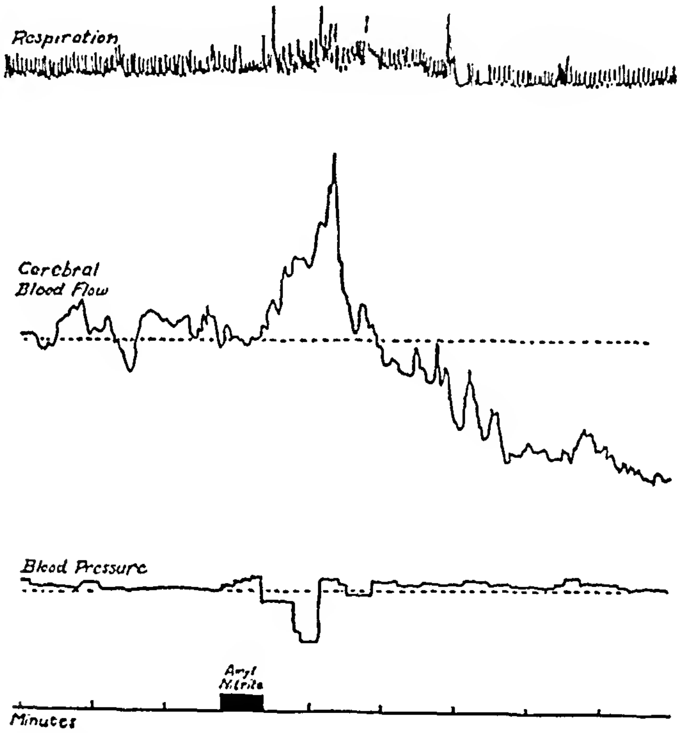

Fig. 3.—Effect of breathing amyl nitrite on cerebral blood flow.
Curves have the same significance as in Fig. 1. During the period marked "amyl nitrite," a crushed ampule was held under the subject's nose. The maximum decrease in blood pressure from the preinjection level was 25 mm. Hg.

blood pressure, whether the total blood flow through the brain increases or decreases can be told only by direct measurement.

In eight instances subjects inhaled the fumes from a crushed amyl nitrite pearl. They were instructed to breathe quietly in order not to introduce the factor of an altered CO_2 content of the blood. Inhalations were discontinued when the characteristic flushing of the face or drop in blood pressure appeared. The results as regards cerebral blood flow were varied. In four instances the blood flow increased, returning to its original level after several minutes. In two instances there was

a temporary rise, lasting less than a minute and followed by a fall. The happenings with respect to the blood pressure were constant: a drop occurred in all. In six of the eight cases the flow increased as the pressure fell, indicating a cerebral vasodilatation. A representative curve is that shown in Fig. 3.

In considering the effect of amyl nitrite and similar general vasodilators, it must be realized that the drop in blood pressure which they produce tends to reduce cerebral blood flow. The fact that there was, in six cases, an immediate increase in flow indicates that the cerebral vessels had dilated sufficiently to permit an increased flow despite the decrease in pressure. In the two cases in which a decrease in flow oc-

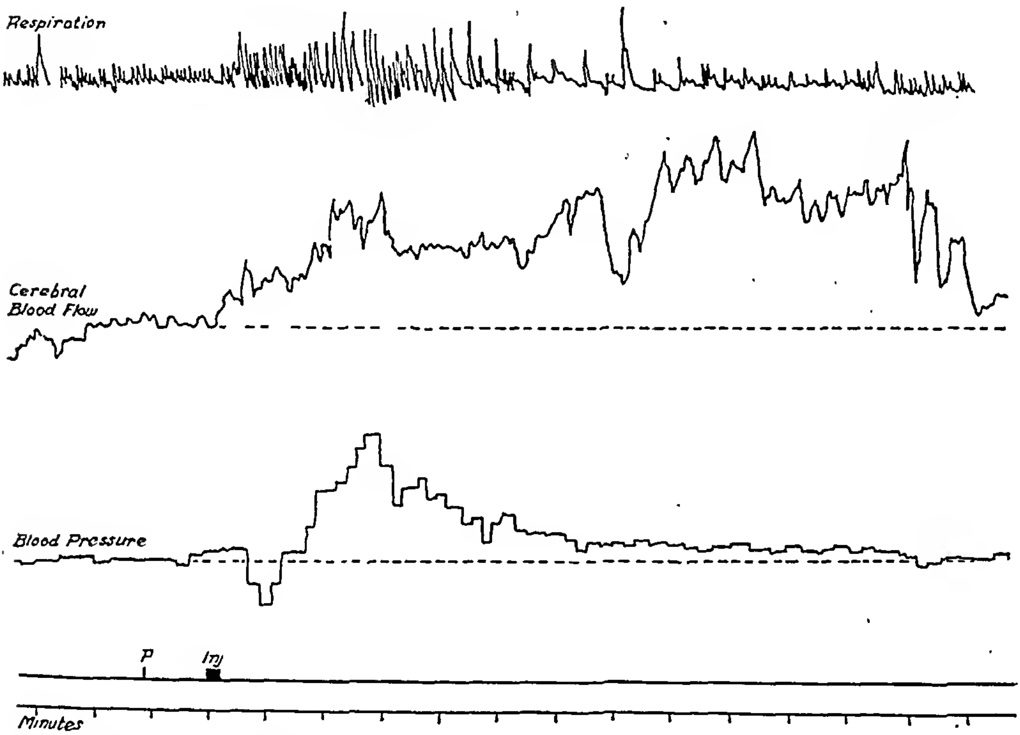

Fig. 4.—Effect of histamine on cerebral blood flow.

Tracings as in Fig. 1. At *P* needle was inserted into an arm vein. During period marked "Inj.," 0.5 mg. of histamine was injected into the blood stream. The maximum increase in blood pressure, above the preinjection level, was 25 mm. Hg.

curred, the cerebral vasodilatation presumably was not complete enough to compensate for the fall in pressure. In these two cases, however, the decrease in flow was not as great as would have been expected had so marked a drop in pressure occurred without an increase in the caliber of the cerebral vessels.

HISTAMINE

The difficulty of accepting animal experiments is shown by the diverse effects on pial vessels dependent on the type of anesthesia used.[10] With amytal anesthesia, injection of histamine caused pial dilatation. More important are the observations that intravenous injection of histamine,

because of the sharp increase in spinal fluid pressure, can be used in human subjects as a measure of circulation time from any vein to cerebral arterioles. Because there is not a corresponding fall in blood pressure, there must be a considerable increase in cerebral blood flow. Weiss and Lennox[11] found this to be true, judging from a decrease in the A-V difference for oxygen in the internal jugular vein blood.

In the single trial of histamine which we made, the result was as expected. The cerebral blood flow increased gradually but steadily for ten to fifteen minutes, then fell rather abruptly to the previous level. In contrast, the blood pressure first fell, then rose, and returned to the normal level while the flow was still increasing (Fig. 4).

SUMMARY

Records of changes in cerebral blood flow were obtained by means of a thermoelectric blood flow recorder introduced into the internal jugular vein of unanesthetized subjects. Simultaneous records were also made of respiration and blood pressure.

Intravenous injection of amounts of adrenalin chloride, sufficient to cause a marked rise in blood pressure, caused a great increase in cerebral blood flow, this increase undoubtedly being secondary to increase in blood pressure. Minute amounts of adrenalin caused a slight rise in flow without change (or with a fall) in blood pressure, suggesting a vasodilator action.

Intravenous injection of caffein sodium benzoate usually caused a decrease in flow, with eventual restoration to a normal or slightly more than normal level. Since this occurred in the face of an invariable rise in blood pressure, a temporary constricting action, perhaps secondary to respiratory stimulation, is indicated.

Inhalation of amyl nitrite produced usually an increase in flow in spite of a decrease in blood pressure, indicating a pronounced dilatation of cerebral vessels.

Intravenous injection of histamine in one case caused a gradual but progressive increase in blood flow, independent of blood pressure changes.

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THE PRECORDIAL ELECTROCARDIOGRAM

I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects*

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In a recent publication from this laboratory[1] a method of obtaining electrocardiograms which represent the potential variations of a single electrode was described. It was shown that a central terminal connected through large and equal resistances to the right arm, the left arm, and the left leg may be regarded as at zero potential throughout the cardiac cycle. When this terminal is paired with an exploring electrode, the curve obtained represents the potential variations produced by the heartbeat at any point with which this electrode is in contact. It is the purpose of this article to describe the curves obtained in a series of normal subjects by leading in this manner from the extremities and from a series of precordial points. An account of the curves obtained in the same way when ventricular hypertrophy or some other type of cardiac abnormality is present will be given in subsequent papers.

The normal precordial electrocardiogram has been studied in some detail by a number of previous investigators.[2-8] All of these have employed precordial leads of the kind introduced by Wolferth and Wood,[2] and the majority have taken leads from a single precordial point. The data which they have collected do not furnish adequate normal standards for the study of abnormal hearts by the method we have used. This study was carried out for the purpose of obtaining such standards.

METHODS

Thirty normal men (medical students) varying in age from twenty to thirty-five years were selected for this study. None of these had ever had symptoms referable to the heart, and none exhibited physical or roentgenographic signs of cardiac abnormality. Teleroentgenograms of the heart and lungs, made by the University Health Service, were available in all cases.† All electrocardiograms were made with the subject in the supine position. Two string galvanometers recording simultaneously on the same film were employed. One of these galvanometers was used in the ordinary way; the other was connected to the balanced plate circuit of a single-stage, vacuum-tube amplifier. The former was used to take standard Lead I simultaneously with each of a series of twelve curves recorded by the latter. The

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†In twenty-five cases the roentgenograms were taken either shortly after or less than ten months before the electrocardiographic study. In the remainder, with one exception, the interval between the electrocardiographic and the roentgenographic examination was less than two years.

first three curves of this series were standard Leads I, II, and III. The second three curves were obtained by pairing the indifferent central terminal with the electrodes on the right arm, left arm, and left leg in succession; these curves will be referred to as extremity potentials and will be designated by V_R, V_L, and V_F, respectively. The last six curves were obtained by pairing the central terminal with an exploring electrode placed in contact with the following precordial points: the fifth rib at the right sternal edge; the fifth rib at the left sternal edge; the fifth intercostal space midway between the left sternal edge and the left midclavicular line; the fifth intercostal space in the left midclavicular line; the sixth rib in the left anterior axillary line; and the tip of the ensiform process. The curves so obtained will be designated by the symbols V_1, V_2, V_3, V_4, V_5, and V_E, respectively. In taking those leads which represent the potential variations of a single point, the connections were so made that relative negativity of the electrode paired with the central terminal produced an upward deflection in the finished record. In the precordial curves a deflection of 1 cm. represents a potential difference of 2 millivolts; all other curves were taken with the galvanometer at normal sensitivity.

The contact surface of the electrode used in taking the precordial leads was roughly circular, and approximately 1 cm. in diameter; this electrode consisted of a small piece of sponge soaked in a strong solution of sodium chloride and thrust into the lower end of a glass tube where it came in contact with a small zinc plate. The skin of the precordium was prepared by vigorously rubbing it with a pad moistened with propanol until erythema appeared. The electrode was held in contact with the skin at the desired point by an assistant.

In six instances the precordial points at which the exploring electrode was placed were marked with small squares of metal held in place with adhesive tape, and a teleroentgenogram was taken with the subject in the supine position (Fig. 1).

THE STANDARD ELECTROCARDIOGRAMS AND EXTREMITY POTENTIALS

Judged by the criteria in general use, the majority of the standard electrocardiograms are well within normal limits. One subject displayed a QRS interval which measured 0.103 second. Another showed a grade of left axis deviation rarely seen in normal subjects; in this instance the index determined by the method of White and Bock[9] was 21.5, and the electrical axis determined by the method of Carter, Richter, and Greene[10] made an angle of –22 degrees with the horizontal. The S deflection measured 0.8 mv. in Lead II and 1.3 mv. in Lead III. In eight other electrocardiograms the voltage of R or S, and in one instance the voltage of T, was outside the normal limits established by Lewis and Gilder,[11] but R exceeded 2.0 mv. in only two instances. The minimum, maximum, and mean voltages of the Q, R, S, and T deflections are given in Table I. This table also gives in each instance the standard deviation and the coefficient of variation, which expresses the standard deviation as a percentage of the mean. The standard deviation is a measure of absolute variability, the coefficient of variation a measure of variability in relation to the magnitude of the mean.

The extremity leads V_R, V_L, and V_F were taken in such a way that a positive variation in potential is represented by a downward, a nega-

tive variation by an upward excursion of the string shadow. As in the case of the precordial leads, the individual deflections have, however, been labelled as if their directions were reversed; i.e., an initial summit is called Q, the inverted peak is called R, and the summit which follows R is called S. Our reasons for adopting this nomenclature are given in a subsequent paragraph. The extremity leads form a connecting link between the standard leads, to which they are closely and directly related,[1] and the precordial leads. For comparison with the latter they are much more useful than the standard leads because each represents the potential variations of a single extremity.

Fig. 1.—Teleroentgenogram of Subject 24 with metal markers on chest wall to show points from which precordial leads were taken. The time of onset of the chief upstroke (RS deflection) in seconds after the earliest QRS deflection in standard Lead I was: V_1, 0.033; V_2, 0.026; V_3, 0.019; V_4, 0.049; V_5, 0.044; V_E 0.027.

Their chief value lies in the relations which they often bring to light between the deflections of the standard leads and the corresponding deflections of the precordial leads.

In the majority of instances the ventricular complexes of the right arm lead begin with a prominent upright or negative deflection (labelled Q in Figs. 2 and 3 and in Table I). In this respect they differ from those obtained from the precordium. An initial downward or positive deflection is present in less than one-half the cases. The frequency with which this deflection is absent is probably due to the circumstance that the attachment of the right arm to the trunk lies

opposite the large valvular orifices at the base of the heart, so that the right arm displays variations in potential similar to those that occur in the ventricular cavities.

In normal subjects the QRS deflections of the left arm are ordinarily very small. The algebraic sum of the largest negative and the largest positive deflection in this lead may be taken as an index of the grade

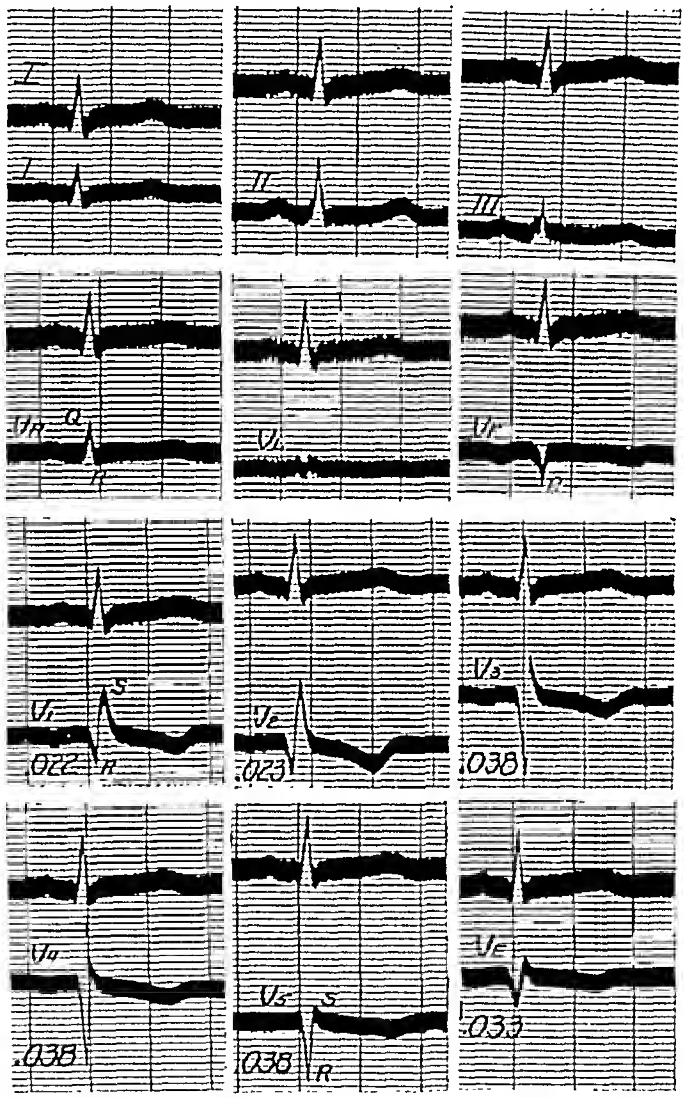

Fig. 2.—Standard leads (I, II, and III), extremity potentials (V_R, V_L, and V_F), and precordial potentials (V_1, V_2, V_3, V_4, V_5 and V_E) of Subject 19 taken simultaneously with standard Lead I (upper string in all curves). Extremity and precordial curves are labelled as if inverted. Time of onset of chief upstroke (RS deflection) is written on each of the six precordial curves. The latter were taken with the string at half the normal sensitivity (1 millivolt=2 cm.). In taking all other curves the string was at the normal sensitivity.

and kind of axis deviation shown by the standard leads. When multiplied by three, the index so obtained closely approaches in value that advocated by White and Bock.[9] Since the deflection in the left arm lead is at all times equal to one-third the deflection in Lead I minus

the deflection in Lead III, the reason is obvious. In our series of cases the average index determined by the method of White and Bock was 2.16; the average index determined from the left arm lead by the method described was 1.84. The largest discrepancy between the two methods encountered amounted to 4.1 units (0.41 mv.).

In general outline the ventricular complexes of the left leg lead usually resemble those inscribed in leads from the left side of the

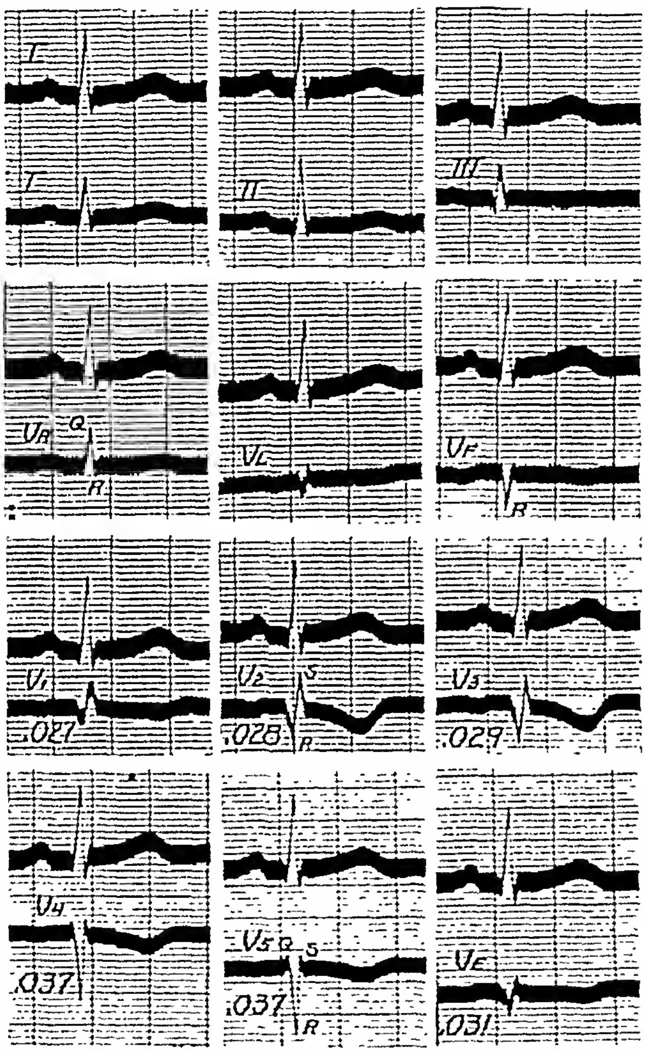

Fig. 3.—The standard leads (I, II and III) extremity potentials (V_R, V_L and V_F) and precordial potentials (V_1, V_2, V_3, V_4, V_5, and V_E) and Subject 4 taken simultaneously with standard Lead I. The figures written on the records give the time of the chief upstroke (RS deflection) *with reference to the beginning of the earliest ventricular* deflection in Lead I. The precordial curves were taken with the string at half the normal sensitivity; the remaining curves with the string at the normal sensitivity.

precordium (V_4 and V_5). When the electrical axis points toward the left leg, the resemblance is much closer than when the axis is more horizontal. When the standard leads display a conspicuous grade of left axis deviation, as in one of our subjects, the complexes of the leg

curve are similar to those obtained from the right side of the precordium, and the complexes of the left arm curve are like those obtained from the left side of the precordium.

The minimum, maximum, and mean values of the Q, R, S, and T deflections of the right arm, left arm, and left leg leads (V_R, V_L, and V_F) are given in Table I. In order to obtain a measure of the resemblance between the left leg curve and the curves obtained from the left side of the precordium, the coefficients of correlation between the amplitude of each of the QRS deflections in lead V_F and the amplitude of the corresponding deflection in lead V_5 were determined. For Q this coefficient was 0.518 ± 0.09; for R, 0.428 ± 0.1; and for S, 0.487 ± 0.094.* While these coefficients do not indicate a high degree of correlation, they show that there is a definite similarity between the QRS deflections of these two leads.

THE PRECORDIAL ELECTROCARDIOGRAM

In studying the precordial electrocardiograms we have confined our attention to the form of the ventricular complex. For the purposes of measuring the P-R and QRS intervals and of investigating the form of the auricular complex, precordial leads do not appear to be more useful than the standard leads.

In general outline the ventricular complexes of precordial leads closely resemble those obtained when the exploring electrode is placed directly in contact with the exposed ventricular surface. In normal curves the QRS group always displays a conspicuous downward movement followed by a sudden upstroke, which ordinarily carries the string shadow beyond the baseline. It has been pointed out that this sudden upstroke, which is produced by a large negative variation of the potential of the exploring electrode, corresponds to the intrinsic deflection of direct leads. It signals the arrival of the excitatory process at the epicardial surface of that portion of the ventricular wall which lies beneath the exploring electrode.

In normal curves from the right side of the precordium the chief upstroke occurs early in the QRS interval and usually rises high above the baseline. The downward deflection which precedes it is relatively small. In normal curves from the left side of the precordium the chief upstroke occurs relatively late in the QRS interval and may or may not rise above the baseline. The downward deflection is relatively large and is not infrequently preceded by a small initial summit.

The QRS group of a normal precordial electrocardiogram may, therefore, display three distinct apices; a preliminary summit, an inverted peak which marks the onset of the chief upstroke, and a final

*The correlation coefficient is a pure number which varies from +1 to −1. When the relation between two variables is perfect and positive, its value is +1. When the relation is perfect but inverse, its value is −1. For calculation of the probable error of the correlation coefficient see final note.

summit which marks the termination of the chief upstroke. The inverted peak is always present, but either or both summits may be absent. Slurring or slight notching of the chief deflections is not uncommon.

For the sake of convenience in description it is desirable that the different deflections inscribed during the QRS interval in precordial leads be designated by letters in the same manner as is customary in the case of the QRS deflections of the standard leads. The use of the letters Q, R, and S for this purpose has certain disadvantages but is, so it seems to us, preferable to the introduction of an entirely new terminology. Since the individual QRS deflections of standard leads do not originate in exactly the same way, and do not necessarily correspond to those of precordial leads either in number or in time, any method of assigning names to the latter must be arbitrary. The method adopted should, if possible, be applicable to abnormal, as well as to normal, curves.

In precordial curves the inverted peak which marks the onset of the chief upstroke is the most constant deflection of the QRS group. Since it corresponds in origin to the intrinsic deflection of direct leads, its recognition is of great importance. In the case of the standard leads it is customary to label a downward deflection "S" when it is preceded by an upward deflection, and "Q" when it is not. If we follow the same plan in labeling precordial curves, the name given to the deflection in question will depend upon whether it is or is not preceded by a small initial summit. Since, however, its origin and its significance are the same in either case, we believe that it should always be designated by the same symbol. We advocate calling this deflection "R," and naming the summit which usually follows it "S." The summit which sometimes precedes it may then be called "Q." In justification of this proposal a few words of explanation are desirable. Some investigators, Groedel[12] for instance, have taken precordial curves in such a way that relative negativity of the exploring electrode is represented in the finished record by a downward instead of by an upward deflection. In comparison with the one we have used this method reverses the direction of all the deflections. It has a number of decided advantages, and it is not unlikely that it will eventually come into general use. It yields precordial curves in which P and T are normally upright, instead of inverted, and in which the QRS deflections also are very similar in general outline to those of the standard leads. It has the further advantage that negativity of the exploring electrode is represented by a downward deflection, positivity of this electrode by an upward deflection—an arrangement which is more conventional than the reverse and which makes it possible to refer to downward deflections as negative and upward deflections as positive without danger of being misunderstood. As we have

already indicated, it greatly simplifies the problem of naming the QRS deflections of normal precordial curves, and permits us to use the letters Q, R, and S in exactly the same manner as in the case of the standard leads.

The method of taking precordial leads which we have used was originally adopted in this laboratory in order to emphasize the similarity in form between human precordial curves and the ventricular complexes of the direct leads employed in animal experiments by Lewis and Rothschild.[13] These were so taken that the intrinsic deflection was represented by an upstroke. The advantages of reversing the polarity of all direct, semidirect, and precordial leads are, however, so great that we believe this policy will eventually be adopted by the majority. For this reason and in order to avoid introducing a new nomenclature, we have labelled the precordial curves of this article as if they were inverted. It seems to us desirable that the individual deflections of the ventricular complex in precordial leads be designated by the same letters by all workers, regardless of whether the left- or the right-hand electrode is placed in contact with the precordium.

THE VOLTAGE OF THE VENTRICULAR DEFLECTIONS IN PRECORDIAL LEADS

The minimum, maximum, and mean voltages of Q, R, S, and T in the precordial leads employed are shown in Table I. An initial summit or Q reflection did not occur in the ensiform lead (V_E) or in either of the first two precordial leads (V_1 and V_2) in a single instance. In the third precordial lead (V_3) such a deflection was present only once, but in the fourth precordial lead (V_4) it occurred ten times and in the fifth precordial lead (V_5), eleven times. The magnitude of the chief deflections, R and S, showed a sort of reciprocal relationship; as the exploring electrode was moved over the precordium from right to left the former tended to become larger, the latter smaller. The average voltage of the R deflection (Table I) increased progressively in the first four precordial leads and was nearly as great in the fifth as in the fourth where it was maximal. On the other hand, the average voltage of the S deflection was nearly as great in the first precordial lead as in the second in which it reached its greatest value. In the leads taken farther to the left it progressively decreased. In the leads from the left side of the precordium this deflection was sometimes absent; three times in the third lead, four times in the fourth, and twelve times in the fifth. In the ensiform lead it was absent twice.

The chief upstroke in precordial leads begins at the apex of R and ends at the apex of S. Its amplitude may be measured directly or may be found by adding (without regard to sign) the voltages of these two deflections. The figure so obtained gives a better idea of the magnitude of the potential variations produced by the heartbeat in a given lead than does the voltage of the largest QRS deflection meas-

TABLE I

THE SIZE OF THE VENTRICULAR DEFLECTIONS IN THE STANDARD AND SPECIAL LEADS (MEASUREMENTS GIVEN IN TENTHS OF A MILLIVOLT)

LEAD	Q					R					S					T					RS				
	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION
I	0	1.5	0.33	0.45	135.1	1.5	19.4	6.81	3.27	48.0	0	5.0	1.67	1.35	81.1	1.0	5.5	2.21	1.05	47.5	3.0	20.6	8.63	3.20	37.1
II	0	2.0	0.43	0.61	140.1	4.0	22.0	11.99	4.39	36.6	0	8.0	1.53	1.92	125.7	1.0	6.0	2.97	1.10	37.0	8.0	23.0	13.76	3.72	27.1
III	0	2.0	0.54	0.60	111.7	1.2	18.0	8.50	4.33	50.9	0	13.0	1.27	2.40	189.1	0	3.0	1.49	0.75	50.4	3.2	18.0	10.12	4.10	40.5
V_R	0	7.6	2.81	2.68	95.7	0	3.0	0.76	0.65	85.0	0	10.5	2.56	3.41	136.5	−3.3	−0.8	−1.66	0.61	36.7	3.5	11.7	6.30	1.82	28.9
V_L	0	1.5	0.21	0.42	195.4	0	7.0	1.13	1.34	118.4	0	7.0	2.00	1.60	80.3	−1.0	1.0	0.05	0.41	825.2	0.5	8.5	3.27	1.85	56.7
V_F	0	1.2	0.29	0.37	127.2	0	13.0	6.68	2.81	42.1	0	6.5	0.80	1.28	160.5	0.2	2.8	1.46	0.62	42.1	4.0	13.0	7.66	2.54	33.2
V_1	0	0	0	0		1.0	9.6	4.16	2.33	56.0	3.4	24.0	11.05	5.03	45.5	−4.0	5.6	1.23	1.88	152.9	6.6	26.8	15.21	5.98	39.2
V_2	0	0	0	0		4.0	20.8	9.05	3.68	40.6	3.0	38.8	16.23	7.30	45.0	2.4	11.0	6.22	1.90	30.6	15.0	46.0	25.27	7.47	29.6
V_3	0	0.4	0.013	0.072	538.6	6.0	54.6	16.70	9.78	58.6	0	22.0	9.05	5.62	62.1	3.6	12.0	6.26	1.89	30.2	12.6	54.6	25.75	8.37	32.5
V_4	0	3.0	0.37	0.68	185.8	12.2	46.0	22.31	7.10	31.8	0	16.0	5.32	4.13	77.6	2.4	11.0	5.66	1.84	32.6	18.0	51.6	27.63	6.71	24.1
V_5	0	3.4	0.57	0.91	161.0	8.8	33.0	18.78	6.91	36.8	0	9.6	1.93	2.22	115.2	2.0	9.6	4.59	1.82	39.7	11.2	33.2	20.70	6.50	31.4
V_E	0	0	0	0		2.0	12.8	5.81	2.49	42.8	0	16.2	6.09	4.78	78.4	0.2	5.2	2.55	1.11	43.5	5.6	24.2	11.91	4.33	36.4

ured from the baseline. When Q is larger than S, the QR downstroke is larger than the RS upstroke, but the difference is seldom great in normal subjects. The latter movement is more abrupt than the former and corresponds to the intrinsic deflection of direct leads. Whenever possible it has, therefore, seemed preferable to take the height of the chief upstroke rather than the amplitude of the largest excursion of the string, regardless of its direction, as a measure of the magnitude of the potential variations of the exploring electrode.

The minimum, maximum, and mean amplitude of the chief upstroke or RS deflection in the various leads employed are given in Table I. In the case of the standard leads and of the right- and left-arm leads a deflection strictly analogous to the intrinsic deflection of direct leads was frequently absent or could not be identified. In such cases the sum of the largest downward deflection and the largest upward deflection was substituted for the amplitude of the chief upstroke or RS deflection.

It will be seen that the RS deflection is on the average considerably larger in the second, third, and fourth precordial leads than in the first or fifth or the ensiform lead. For this difference several factors may be responsible, but we believe that the distance of the exploring electrode from the heart is the most important. There is a striking falling off in the amplitude of the ventricular deflections when the distance of this electrode from the heart is increased. For this reason the amplitude of the chief upstroke is three and one-half or four times as large in the midprecordial leads (V_2, V_3, and V_4) as in the extremity leads (V_R, V_L, and V_F) and two or two and one-half times as large as the largest excursions of the string seen in the standard leads. The large size of the RS deflection in the second, third, and fourth precordial lead is probably due, therefore, to the nearness of the exploring electrode to the heart's surface.

The question arises whether there is any relation between the amplitude of the QRS deflections in the precordial leads and the amplitude of these deflections in the standard leads. In order to answer this question, we have determined the coefficient which measures the correlation between the magnitude of the RS deflection in the fourth precordial lead and the greatest excursion of the string shadow (R plus S or R plus Q) in Lead II. For our series of cases this coefficient is 0.429 ± 0.1. We also determined the correlation coefficient for the largest RS deflection in any precordial lead paired with the largest excursion of the string in any standard lead; this coefficient is 0.458 ± 0.097. It seems, therefore, that the size of the QRS deflections in the standard leads and the size of these deflections in the precordial leads tend to vary in a parallel manner, but that no very close relation exists.

The junction of the last deflection of the QRS group with the final deflection of the ventricular complex (the S-T junction) usually occurred very close to the baseline, and the voltage that separated it from this line was never greater than 0.15 mv. This voltage was usually positive; it was negative in only eight instances. The portion of the ventricular complex lying between the S-T junction and the apex of T was sometimes represented by a straight line, but more often by a curve slightly convex toward the baseline.

In all precordial leads, except the first, the potential of the exploring electrode during the inscription of T was invariably positive, and, in our curves, this deflection was therefore downward. In the first precordial lead, however, T was upright in three instances. The average voltage of T was greatest in the second and third precordial leads (V_2 and V_3) and showed a progressive decrease in the leads taken farther to the left. It was smallest in the first lead (V_1). In tabulating measurements of the T deflection, T-waves which were upright in our curves were considered negative and inverted T-waves, positive; during the inscription of the former the potential of the exploring electrode was negative; during the inscription of the latter it was positive.

Whether the form of the ventricular complex is more variable in precordial than in the standard leads, or vice versa, is a question that is difficult to answer. We have attempted to obtain some exact information on this point by computing the standard deviations and the coefficients of variation of the amplitudes of the various deflections in each lead. The standard deviation or root-mean-square deviation from the mean is the standard measure of absolute variability, but it is not suitable for comparing the variability of quantities which differ widely in average magnitude or which are measured in different units. To overcome this difficulty statisticians introduced the coefficient of variation, which expresses the standard deviation as a percentage of the mean. It is supposed to measure relative variability and is a pure number, and, therefore, not dependent upon the unit of measurement. While it may be a satisfactory measure of relative variability under certain conditions, it is wholly unsatisfactory in the present circumstances.

It is obvious that when the variates may take negative as well as positive values, as in the case of the voltage of the T-wave in certain leads, the mean is likely to be absolutely small and may be zero. In the latter case the coefficient of variation becomes infinite, even though the standard deviation is small. A similar situation arises when a considerable number of the variates are zero. The Q deflection in the third precordial lead, for example, was absent in twenty-nine instances out of thirty. The mean amplitude of this deflection was, therefore, very small and the coefficient of variation, very large. We

would not ordinarily, however, think of a deflection which had the same value, in this case zero, in all but one instance as highly variable. In all those instances in which the minimum amplitude of the variate is zero or negative, the coefficient of variation must be regarded as practically meaningless for our present purpose. While its failure under these circumstances casts some doubt upon its value in the remaining instances, no more satisfactory measure of relative variability is available.

When the deflections of the precordial leads are compared with the corresponding deflections of the standard leads, it will be seen that the coefficients of variation are not, as a rule, materially larger in the one case than in the other. It should be noted that very bizarre QRS groups, such as are frequently seen in standard Lead III, rarely if ever occur in precordial leads in normal subjects.

For a few deflections we determined the third and fourth moments about the mean and computed the skewness and the excess or measure of kurtosis. The skewness of the distribution was positive in all instances, and it was sometimes large; the excess was sometimes negative, sometimes positive, and in the latter case occasionally very large. Because the number of variates in each array is only thirty, however, the statistical constants that depend upon the higher moments have a very large probable error. We concluded that the information to be gained from them would not justify the labor that computing them would require. It is clear that the difference between the mean and the maximum amplitude of a given electrocardiographic deflection is almost always considerably greater than the difference between the mean and the minimum amplitude.

TIME OF ONSET OF THE CHIEF UPSTROKE (RS DEFLECTION)

It has already been pointed out that the chief upstroke or RS deflection occurs earlier in leads from the right side of the precordium than in leads from the left side. The interval from the beginning of the earliest QRS deflection in Lead I to the onset of the chief upstroke in each precordial lead was carefully measured.* The minimum, maximum, and average values of this interval for each of the six precordial leads employed are given in Table II. The first QRS deflection of Lead I does not necessarily occur at the very beginning of the QRS interval, nor does it always occupy in different subjects exactly the same position in this interval. For this reason the values of the interval in question for the different precordial leads show a considerable degree of correlation, one with another. When the value of this interval in the first was paired with its value in the fifth precordial lead, the correlation coefficient was found to be 0.73 ± 0.057.

*The measuring machine devised by Captain Elliott and manufactured by the Cambridge Company was used for this purpose.

When the mean value of this interval in the first two precordial leads (V_1 and V_2) was paired with its mean value in the fourth and fifth, the correlation coefficient was 0.67 ± 0.069. It is clear, therefore, that the absolute magnitude of the figures given for the different leads are much less significant than their relative magnitude. The smallest difference in time between the earliest and the latest chief upstroke in the same subject measured 0.008 second; the largest, 0.03 second. This difference in time exceeded 0.025 second in only six instances; its mean value for our series of cases was 0.0194 second. On the average the chief upstroke began about 0.016 second earlier in the first two precordial leads than in the fourth and fifth (V_4 and V_5). The average figures for the two leads of the first pair are very much alike, and the same is true of the average figures for the two leads of the second pair. The average figure for the ensiform lead and that for the third precordial lead have an intermediate value, but the former is similar to the figures for the first and second precordial leads while the latter is similar to the figures for the fourth and fifth.

TABLE II

TIME OF ONSET OF THE CHIEF UPSTROKE (RS DEFLECTION) WITH REFERENCE TO THE EARLIEST VENTRICULAR DEFLECTION OF LEAD I

LEAD	MINIMUM SECONDS	MAXIMUM SECONDS	MEAN SECONDS	STANDARD DEVIATION SECONDS	COEFFICIENT OF VARIATION (PER CENT)
V_1	0.006	0.033	0.0172	0.0064	37.0
V_2	0.003	0.039	0.0193	0.0085	44.0
V_3	0.013	0.049	0.0314	0.0097	30.9
V_4	0.023	0.055	0.0349	0.0075	21.5
V_5	0.023	0.053	0.0336	0.0074	22.0
V_E	0.006	0.048	0.0249	0.0104	41.7
Difference between shortest and longest interval	0.008	0.030	0.0194	0.0057	29.4

The reason for this grouping apparently lies in the relation of the exploring electrode in its different positions to the anterior surfaces of the two ventricles. It has been pointed out in previous papers that the ventricular deflections of a given precordial lead are usually similar in general outline to those which would be inscribed in direct leads from that portion of the ventricular wall that lies beneath the exploring electrode. It would be anticipated that leads from the right side of the precordium would show an early chief upstroke corresponding to the early intrinsic deflection seen in direct leads from the ventral surface of the right ventricle and that leads from the left side of the precordium would show a late chief upstroke corresponding to the late intrinsic deflection seen in direct leads from the ventral surface of the left ventricle.

In taking a precordial lead defined by the landmarks of the anterior chest wall, the relation of the precordial electrode to the two ven-

tricles naturally varies from subject to subject. In six instances the points where this electrode was applied were marked by small pieces of metal fixed to the chest wall with adhesive tape, and a teleroentgenogram (Fig. 1) was taken with the subject in the supine position, in which the electrocardiographic study was made. It was found that minor errors in placing the electrodes were sometimes made so that they did not always bear exactly the same relation to the bones of the thoracic cage. For this reason and because of the differences between subjects with respect to the height of the diaphragm and the position of the heart, the relation of the metal markers to the boundaries of the cardiac shadow showed considerable variation. In five of the cases studied, the images of the markers corresponding to the ensiform lead and to the first three precordial leads were wholly or partly superimposed upon the cardiac silhouette. In one instance in which the heart shadow was vertically placed, the marker for the third precordial lead fell just outside its left margin. In the case of the subject who showed an unusual degree of left axis deviation, the marker for the fourth precordial lead was partly superimposed upon the shadow of the apex; in all other instances the fourth and fifth markers fell well outside the boundaries of the cardiac image. It is not possible accurately to mark the position of the atrioventricular or of the interventricular groove upon the cardiac silhouette. Nevertheless, the position of the markers with reference to the cardiac shadow suggests that in taking the first two precordial leads and the ensiform lead the exploring electrode was usually placed over the right ventricle. The fourth and fifth precordial leads and in most instances the third as well must be regarded as semidirect leads from the surface of the left ventricle. In taking the third precordial lead, more rarely in taking the second, the exploring electrode was undoubtedly sometimes placed approximately over the interventricular sulcus so that a semidirect lead from both ventricles was obtained.

An x-ray film which shows the relation of the markers to the cardiac silhouette in one of our subjects is reproduced in Fig. 1. The figures which define the position of the chief upstroke in each lead are given in the legend. In the first two precordial leads and in the ensiform lead this upstroke began approximately 0.03 second after the first ventricular deflection in Lead I, while in the last three precordial leads (V_3, V_4, and V_5) it began approximately 0.05 second later.

When the exploring electrode was moved over the precordium from right to left, the change from an early to a late chief upstroke was often abrupt. In twenty-three of the thirty subjects examined, the first late chief upstroke occurred in the third precordial lead; in two cases it occurred in the second and in five cases in the fourth. When the chief upstroke was distinctly notched, it was usually found that the notch was simultaneous or nearly simultaneous with the onset of the chief upstroke in leads taken farther to the left. Notches that

occurred before the onset of the chief upstroke were usually simultaneous with the onset of the chief upstroke in leads taken farther to the right. This suggests that, in precordial leads at least, notches are frequently produced by the difference in time between the activation of the right and the activation of the left ventricular surface.

TABLE III

LEAD	1 NUMBER OF CASES IN WHICH FIRST LATE CHIEF UPSTROKE OCCURRED	2 NUMBER OF CASES IN WHICH R FIRST EXCEEDED S	3 NUMBER OF CASES IN WHICH CHIEF UPSTROKE WAS MAXIMAL	4 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 1 AND 2	5 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 1 AND 3	6 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 2 AND 3	7 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 1, 2, AND 3
V_1	0	1	0	0	0	0	0
V_2	2	3	7	1	0	0	0
V_3	23	18	8	16	8	7	6
V_4	5	7	12	4	1	2	1
V_5	0	1	3	0	0	0	0
V_E	0	(omitted)	0	--	0	-	-
Totals	30	30	30	21	9	9	7

In Table III the first column gives the number of times each precordial lead was the lead farthest to the right in which the chief upstroke occurred late and approximately at the same time as in leads taken more to the left. The second column gives the number of times that each lead was the lead farthest to the right in which the positive deflection R was larger than the negative deflection S. The ensiform lead is here omitted from consideration. In normal subjects this lead is not a particularly favorable one; the QRS deflections are usually small, and in many instances R is larger than S when the opposite is true in other leads from the right side of the precordium. The third column gives the number of instances in which the chief upstroke reached its maximal amplitude in each lead. The last four columns show the number of instances in which each two and all three of the characteristics in question occurred together in each lead. It will be seen that there was a definite tendency for the first late upstroke to occur in the first lead in which R was larger than S, but no particular tendency for the first late chief upstroke to exceed the others in amplitude.

SUMMARY

Using a method which makes it possible to obtain electrocardiograms that represent the potential variations of a single electrode, a study of thirty normal subjects was carried out. The three standard leads and nine special leads were each taken simultaneously with Lead I. Three of the special leads recorded the potential variations of the right arm, left arm, and left leg, respectively; the others recorded the potential variations of a series of six precordial points.

The special curves were taken in such a way that negativity of the exploring electrode, placed upon one of the extremities or upon the precordium, produced an upward deflection in the completed record. It is, however, pointed out that several advantages might be gained by making the connections in the opposite way. For this reason, and to avoid introducing a new nomenclature, our special leads have been labelled as if the direction of the deflections were reversed.

In precordial leads the QRS group may normally show three distinct apices, which for convenience in description may be called "Q," "R," and "S." The R peak, which represents a positive variation in the potential of the exploring electrode and is therefore inverted in our records, is always present. This peak marks the beginning of a large and rapid excursion of the string which corresponds to the intrinsic deflection of direct leads from the ventricular surface. In leads from the right side of the precordium R is smaller and, on the average, reaches its apex about 0.02 second earlier than in leads from the left side. This indicates that, as a whole, the epicardial surface of the ventral wall of the right ventricle is activated earlier than the corresponding surface of the left.

In our records Q and S are both summits. The former is always small in normal subjects and occurs only in leads from the left side of the precordium. The latter is larger on the right side of the precordium than on the left where it may be absent. When the exploring electrode is placed at or to the left of the sternal edge, its potential is invariably positive during the inscription of the T deflection. When the exploring electrode is placed to the right of the midline, the direction of T is variable.

The leads which represent the potential variations of the extremities are related both to the standard leads and to precordial leads and are useful in comparing the one with the other. When the standard leads are of the normal type, the left leg curve usually resembles those obtained from the left side of the precordium, and the deflections of the left arm curve are small.

The authors wish to express their appreciation to Dr. Frank N. Wilson for his help, particularly in the preparation of the paper.

NOTE.—The probable errors of the correlation coefficients given in this article were obtained by application of the formula

$$\text{P.E.}_r = \pm 0.6745 \frac{1 - r^2}{\sqrt{N}}$$

in which N is number of variates and r the coefficient of correlation. In the present instance N equals 30. The probable error of the mean values given may be obtained by the formula

$$\text{P.E. of mean} = \pm \frac{0.6745\ \sigma}{\sqrt{N}}$$

in which σ is the standard deviation.

(See Pearl, *Medical Biometry and Statistics*, ed. 2, Philadelphia, 1930, W. B. Saunders Co.)

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ELECTROCARDIOGRAPHIC ABNORMALITIES CHARACTERISTIC OF CERTAIN CASES OF ARTERIAL HYPERTENSION*

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IN THE course of an investigation into the serial electrocardiographic changes following upon acute coronary occlusion, one of us (H. E. R.) found a number of cases showing abnormalities of the ventricular complexes (QRST) of an unusual type. In certain respects the abnormalities observed in the records of these cases simulated, and in other respects differed from the typical electrocardiographic changes found in myocardial infarction. Further, it was found that without exception all of these atypical records showed an identical type of electrocardiographic abnormality. On examining the histories of this small group of patients, it appeared that a diagnosis of coronary thrombosis had, in each case, been made largely on this electrocardiographic abnormality and that the clinical histories, while in some cases suggestive, in practically all gave but inconclusive support to that diagnosis. Attention was further attracted to these patients when it was observed that all had arterial hypertension at the time when these electrocardiographic records were made. In view of these observations, it seemed desirable to differentiate the electrocardiographic changes observed from the typical changes of coronary thrombosis and also to determine by means of clinical study the nature of the relationship, if any, of the electrocardiographic changes to coronary thrombosis and to arterial hypertension.

CHANGES OF VENTRICULAR COMPLEX

In Figs. 1 to 10, electrocardiograms of the type to be discussed are shown. These records which exhibit almost identical features were obtained from ten different patients who were selected at random from the 143 cases upon which the clinical study is based. The distinctive features of these curves may be described as follows:

The T-wave in the first lead is always a negative deflection and is of the so-called coronary type, being shouldered and having a sharp apex angle. In the third lead the T-wave invariably presents the reverse appearance to that of T_1: it is always a positive deflection, and in the majority of our records the amplitude of T_3 is abnormally in-

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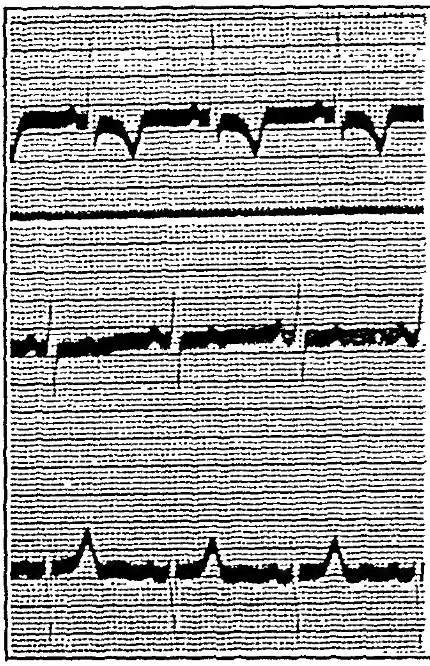


Fig. 1.

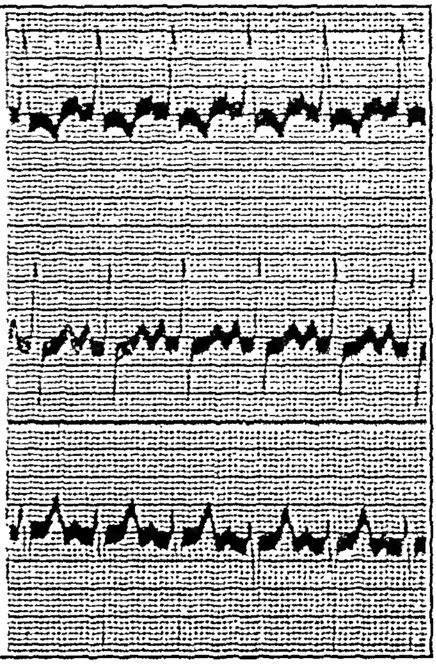


Fig. 2.

Fig. 1.—Case 26. Three usual leads. Blood pressure 180/110. Diagnosis: chronic myocarditis, degenerative; angina pectoris; cardiac hypertrophy.

Fig. 2.—Case 85. Leads I, II, and III. Blood pressure 260/140. Diagnosis: malignant hypertension; chronic myocarditis, degenerative; cardiac hypertrophy.

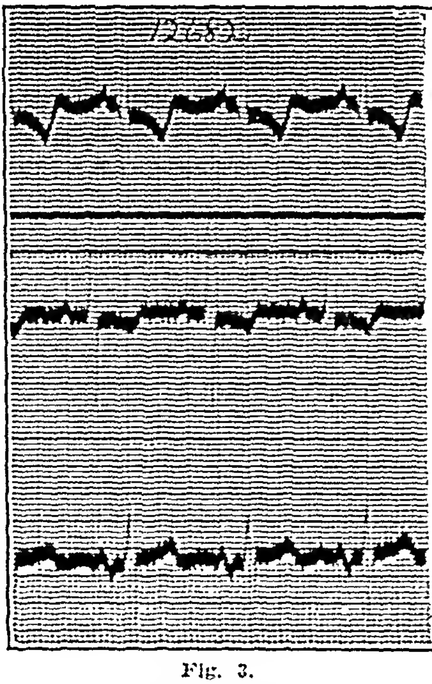


Fig. 3.

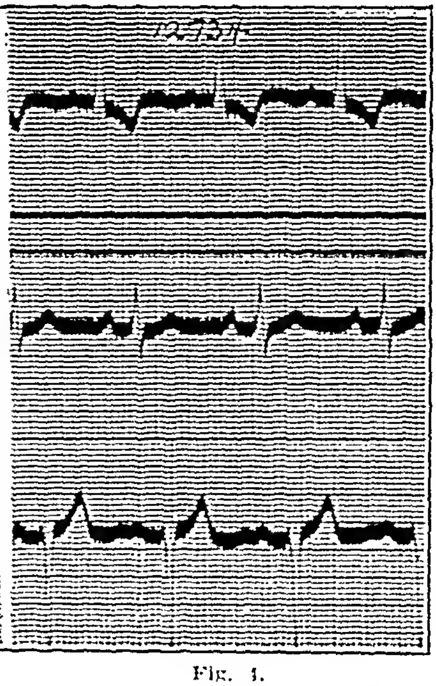


Fig. 4.

Fig. 3.—Case 135. Blood pressure 216/120. Diagnosis: chronic myocarditis, degenerative; cardiac hypertrophy; cardiac insufficiency.

Fig. 4.—Case 139. Blood pressure 224/128. Diagnosis: chronic myocarditis, degenerative; cardiac hypertrophy; chronic nephritis.

creased. The T-wave in Lead II may be a positive, diphasic, or negative deflection. When negative, T_2 may resemble T_1 in contour.

In addition to the T-wave abnormalities, these records show a characteristic type of alteration of that segment of the isoelectric line which lies between the R- or S-waves and the T-wave—the RT or ST segment. In Lead I the RT segment in this type of record is constantly displaced below the level of the isoelectric line. This displacement is not less than 1 mm. and is seldom greater than 2.5 mm. It is never so marked as may be the early RT deviation in the typical T_1 or T_3 type of tracings of coronary thrombosis. In the third lead the RT or ST interval is, in the

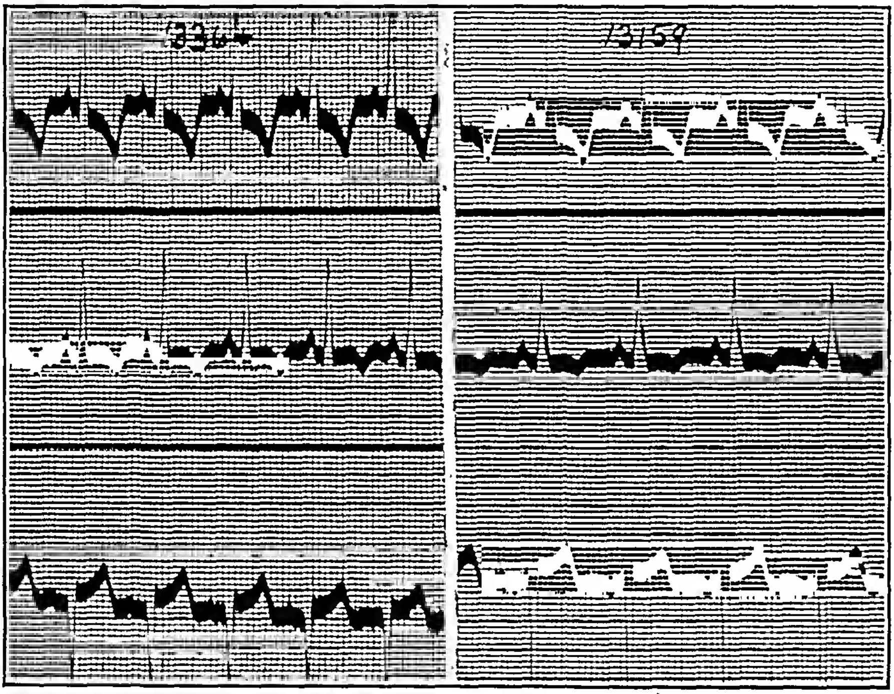


Fig. 5. Fig. 6.

Fig. 5.—Case 29. Blood pressure 206/120. Diagnosis: chronic myocarditis, degenerative; cardiac hypertrophy; angina pectoris.

Fig. 6.—Case 84. Usual leads. Blood pressure 240/140, 190/140. Diagnosis: malignant hypertension; chronic myocarditis, degenerative; cardiac hypertrophy; hemiplegia.

majority of records, elevated above the isoelectric potential. Rarely, however, as in Figs. 1 and 2, the RT segment in the third lead may appear to be almost isoelectric. In Lead II the RT interval may be isoelectric or may exhibit a variable abnormality. Abnormal left axis deviation of marked degree is present in all records of this type. The maximum positive deflection occurs in the first, and the maximum negative deflection in the third lead of these electrocardiograms. In the greater number of these records the voltage of the QRS complexes in Leads I and III was materially increased, and in none was a voltage of less than 1 millivolt observed.

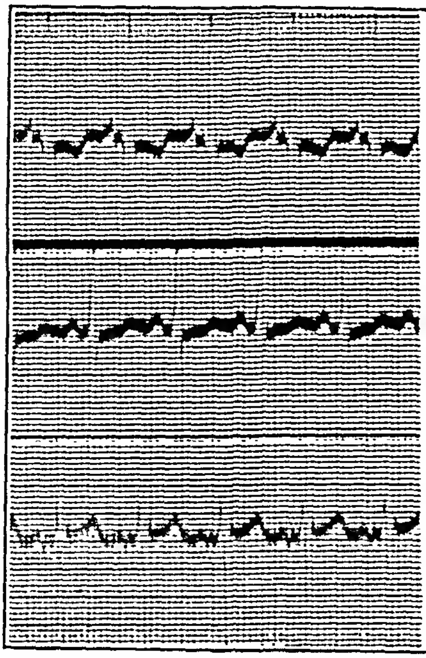


Fig. 7.

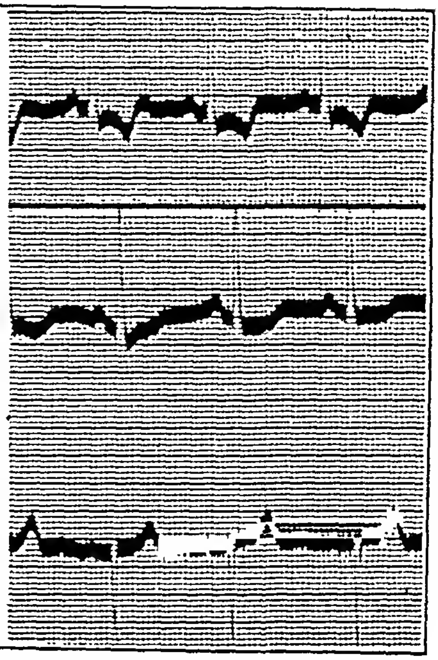


Fig. 8.

Fig. 7.—Case 7. Blood pressure 180/110. Diagnosis: chronic nephritis; chronic myocarditis, degenerative; cardiac hypertrophy; uremia.

Fig. 8.—Case 129. Blood pressure 280/116. Diagnosis: intermittent claudication; cardiac hypertrophy; chronic myocarditis, degenerative.

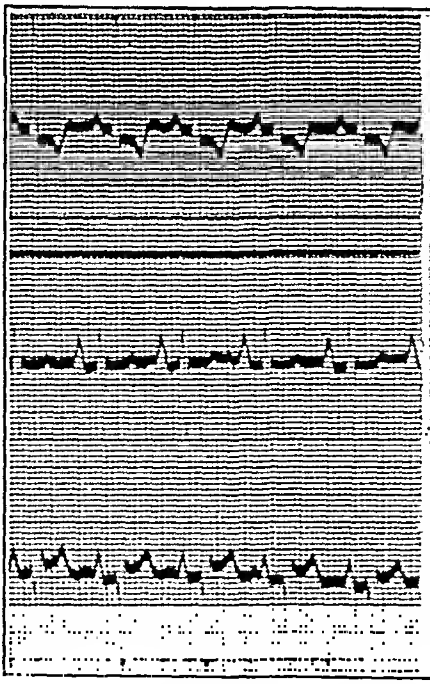


Fig. 9.

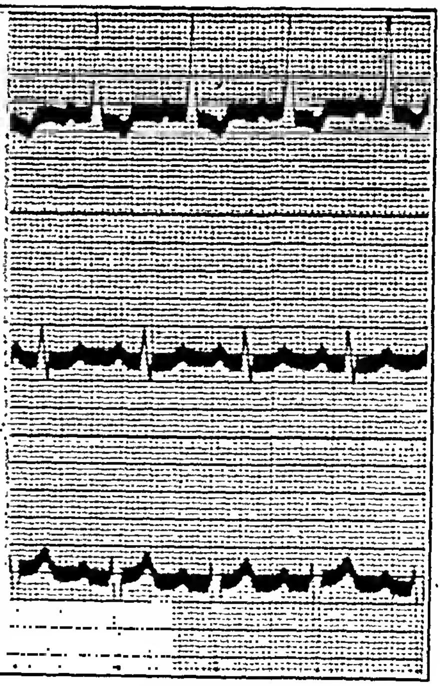


Fig. 10.

Fig. 9.—Case 80. Blood pressure 194/110. Showing changes similar to Figs. 1-8, occurring in a patient who had coronary thrombosis one week before this record was taken. Subsequent serial electrocardiogram showed no significant alteration of the ventricular complexes.

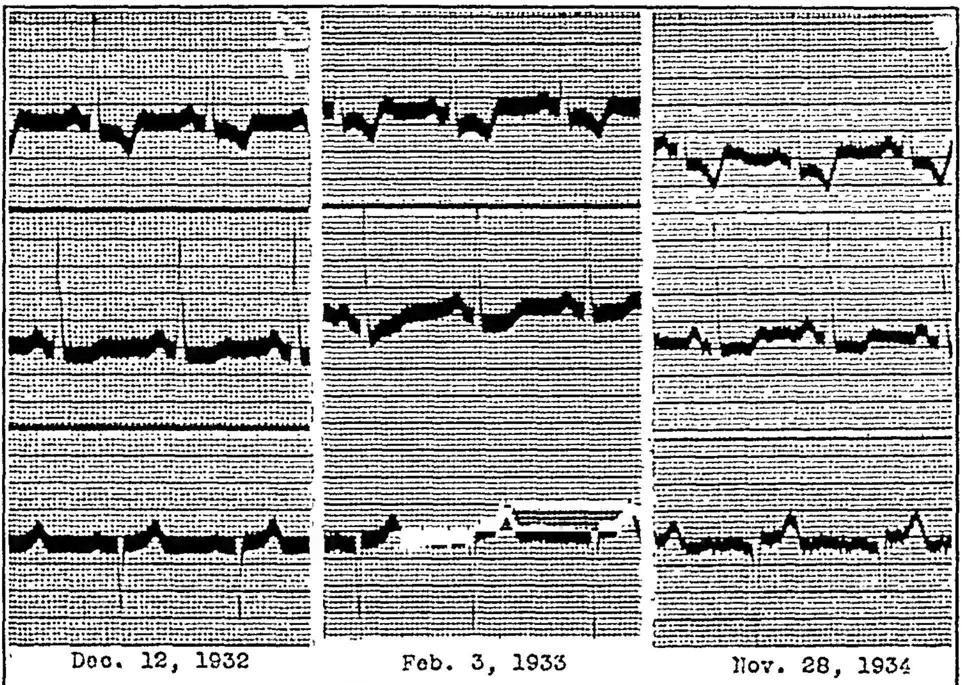
Fig. 10.—Leads I, II, and III, showing similar type of change in a patient with normal blood pressure who had sclerotic aortic stenosis. Electrocardiograms of this type were rarely observed in the absence of hypertension.

Intraventricular conduction time, as estimated by the width of the QRS base, never measures more than 0.10 second and in most electrocardiograms measures less than 0.08 second. Intraventricular conduction defects, therefore, can be definitely excluded, and the presence in these records of abnormal RT deviation and T-wave deflection cannot be explained on the basis of a branch-bundle lesion.

COMPARISON OF ELECTROCARDIOGRAMS SHOWING CHANGES DESCRIBED WITH TYPICAL ELECTROCARDIOGRAMS OF MYOCARDIAL INFARCTION

The three electrocardiograms shown in Fig. 11A were obtained from a patient who had arterial hypertension, degenerative heart disease, and intermittent claudication. The first of these three electrocardiograms was taken upon the entry of the patient into hospital; the second was taken two months later; and the third two years later. These three records are identical and present the abnormal features under discussion. The electrocardiograms in Fig. 11B were taken from a patient who had the typical clinical syndrome of acute coronary occlusion. They present the characteristic electrocardiographic abnormalities of coronary thrombosis of the T_1 type. These records were obtained three hours, ten days, and three months, respectively, after the onset of the substernal pain. Upon comparing these two series of records (Figs. 11A and 11B), it will be observed that the late T-wave changes in coronary thrombosis simulate in certain respects the T-wave changes in the records from the hypertension patient. In both, the T-wave in Lead I is a sharply negative, shouldered deflection, while in Lead III the T-wave is a positive deflection of increased amplitude. In other respects, however, these two series of electrocardiograms are entirely dissimilar. Although taken at intervals of many months, the records obtained from the hypertension patient show no significant alteration of the ventricular complexes. In this regard these three electrocardiograms (Fig. 11A) differ markedly from those obtained from the patient who had myocardial infarction. The latter are characterized by the occurrence of a rapid sequence of changes in the ventricular complexes (QRST). The RS-T displacement in these, as in the typical early records of coronary thrombosis is an evanescent abnormality. As was demonstrated by Parkinson and Bedford,[1] the displacement of the RS-T segment may occur within a few hours of myocardial infarction. This may persist for a variable period, but in the average case the RT interval returns to isoelectric potential within fourteen to twenty-one days. In this respect the electrocardiograms of myocardial infarction are entirely unlike those derived from our series of hypertensive patients. As may be observed from Fig. 11A, the RS-T change which was present in Leads I and III of the initial record persisted and remained unaltered in subsequent records. This has been a constant and characteristic finding. Furthermore, the rela-

Fig. 11A.



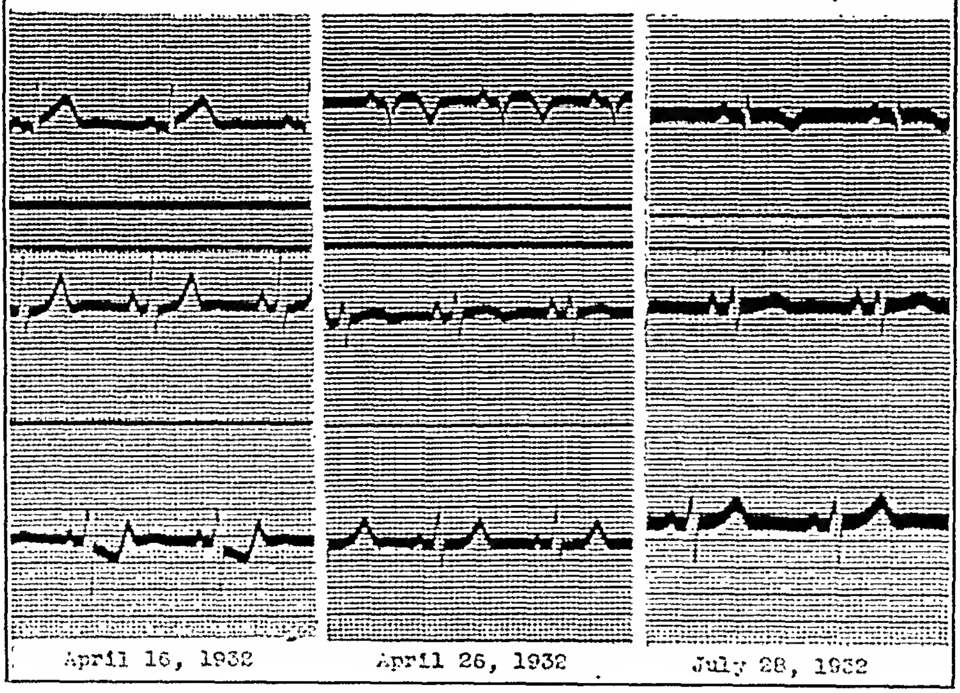


Fig. 11B.

tionship of the RS-T displacement to the T-wave deflection differs in these two series of electrocardiograms. In coronary thrombosis the RS-T deviation in Leads I and III occurs in a direction opposite to the T-wave deflection which develops later. Thus, in the T_1 type of record

the early upward displacement of the RT interval in Lead I is followed by an inversion of the T-wave in that lead. The reverse of this relationship of the RS-T segment to the T-wave is found in the records under discussion. The direction of the displacement of the RS-T segment in Leads I and III (Figs. 1 to 10 and Fig. 11A) conforms to the direction of the T-wave deflection so that in Lead I the RS-T segment takes off below the isoelectric potential and T_1 is a negative deflection, while in Lead III the RS-T interval is elevated above the isoelectric potential and T_3 is a positive deflection.

Another distinguishing feature of the electrocardiograms of this group of hypertensive patients is to be found in the T-wave deflection. In coronary thrombosis during the two to three weeks following the onset of the typical symptoms, the T-wave in Lead I or Lead III, depending upon the type, rapidly changes in form and amplitude. This T-wave change after a variable time may become stationary and persist indefinitely, or it may regress and eventually the electrocardiograms may return to normal. No such change in the form of the T-waves has been observed in the type of record under discussion. From a preliminary study, it would appear that when once established the T-wave and the RS-T defects described persist and remain unaltered until the death of the patient.

In part, the above combination of electrocardiographic defects has been described by Luten and Grove[2] in relation to hypertension. These observers, selecting electrocardiograms showing left axis deviation, T_1 negative, T_3 positive, and QRS of normal width, found that "in 70 per cent of 237 cases a reading at least as high as 170 mm. Hg had been recorded." Also, in a somewhat similar study Master[3] recorded the frequency of T-wave negativity, left axis deviation, and high voltage in electrocardiograms obtained from hypertensive patients. In neither of these reports, however, were alterations of the RT segment commented upon although in Fig. 2 of Luten and Grove electrocardiograms 1 and 3 show the significant changes in the RT segment here described.

CASES STUDIED

The present study was undertaken in order to determine the clinical interpretation of the unusual modification of the ventricular complexes referred to above. All electrocardiographic records taken at the Toronto General Hospital from 1921 to the end of 1932 were reviewed, and 152 out of a total of approximately 7,000 patients suffering from all forms of heart disease were found to have shown electrocardiographic changes conforming with the type described. The clinical histories of these patients, together with available autopsy data, were then reviewed. Those patients who had been discharged from hospital were followed through the out-

patient clinic, and patients known to be alive were brought back to hospital for further examination. In nine of the 152 cases many details of the history and physical examination were lacking. Therefore these cases were excluded and this report is based upon a study of the remaining 143 cases.

SYMPTOMS

It was found that cardiac symptoms predominated in this group of cases. Detailed histories were obtained in 126 of the 143 cases. In 95 the chief complaints were referable to the heart, and in only 5 of the 126 cases was a history of cardiac symptoms not obtained. Dyspnea on exertion, usually of long duration and of increasing severity, was the outstanding symptom and was present in 118 of the 126 cases. Less frequent was dyspnea of a nocturnal or paroxysmal type, which was observed in but 19 cases. Edema of the legs was reported in 60 cases. In 16 cases a history of a prolonged attack of substernal, precordial, or epigastric pain justified a diagnosis of coronary thrombosis, and in 2 of the 16 cases this diagnosis was proved to be correct by a post-mortem examination. Typical attacks of angina pectoris occurred in 28 patients. Cerebral symptoms, such as vertigo, irritability, loss of memory and insomnia, were common, being present in 74 of the 126 cases. Cerebral accidents, either hemorrhage or thrombosis, occurred in 20 cases. Urinary symptoms were rarely complained of although a history of nycturia was obtained in 62 cases.

AGE AND SEX

The average age of all patients was 55.8 years, 86 being males and 57 females. In Table I the cases are divided into age groups according to the presence or absence of hypertension. From Table I it will be noted that this electrocardiographic abnormality was of rare occurrence in patients under the age of forty years and was most frequently present in patients who had reached the sixth and seventh decades of life. Of

TABLE I

AGE OF PATIENT IN YEARS	NUMBER OF PATIENTS WITH H.B.P.		NUMBER OF PATIENTS WITH NORMAL B.P.
20-29	2		3
30-39	4		3
40-49	16		2
50-59	50		4
60-69	38		2
70-79	11		5
Total number of cases	124	+	19 = 143

6 patients under forty years of age who had hypertension, 4 had chronic nephritis, and 2 had malignant hypertension. None of the 6 had endocardial disease. These are to be compared with the 6 patients under

forty years of age who did not have hypertension. All 6 had aortic insufficiency, which was associated in 4 cases with aortic stenosis and in 2 cases with mitral stenosis.

CLINICAL FINDINGS

The remarkably high incidence of arterial hypertension among these patients was the important finding of the present study. Of 143 patients in the series, 124 (86.7 per cent) had arterial hypertension at the time the electrocardiographic records were obtained. In Table II the systolic and diastolic blood pressures of the hypertensive cases are recorded. These observations, in the majority of cases, were made while the patients were at rest in bed in the hospital. For the purposes of this study the patient who had a systolic blood pressure of 160 mm. Hg, or higher, was considered to have arterial hypertension. As will be seen from Table II, 83 (58.0 per cent of the whole series) had a systolic pressure of 200 mm. Hg, or over, and in 41 cases (28.7 per cent) the systolic pressure varied between 160 and 200 mm. Hg. The diastolic pressure readings were correspondingly high. In 67 cases (46.8 per cent) the diastolic pressure was found to be above 120 mm. Hg; in 40 cases (27.9 per cent) it was between 100 and 120 mm. Hg; and in only 17 cases was the diastolic pressure recorded below 100 mm. Hg.

In 19 of the 143 cases (13.3 per cent) the systolic pressure was found to be below 160 mm. Hg. In 7 of these 19 cases a systolic blood pressure of 150 mm. Hg was recorded on at least one occasion. In the remainder the systolic blood pressure varied between 100 and 142 mm. Hg. One patient who had aortic stenosis had on one examination a blood pressure of 130/110. Other readings on the same patient were 120/80 and 100/80, respectively. Three of these 19 patients had a diastolic pressure of 90 mm. Hg, and in the remainder the diastolic pressures were below this figure.

TABLE II

SYSTOLIC BLOOD PRESSURE MM. HG	NUMBER OF CASES	DIASTOLIC BLOOD PRESSURE MM. HG	NUMBER OF CASES
250-300	19	Over 160	5
225-249	17	140-159	22
200-224	47	120-139	40
180-199	31	100-119	40
160-179	10	Less than 100	17
Number of cases			124
Number of cases with normal blood pressure			19
Total number of cases			143

In all patients a diagnosis of myocardial disease was made. As was to be expected from the advanced age of the group as a whole, the incidence of degenerative heart disease was naturally high. Of the 143

patients studied in the series, 126 (88 per cent) had chronic degenerative heart disease. Eight patients had degenerative myocardial disease which was considered to be secondary to syphilitic aortic disease. Chronic rheumatic myocarditis was present in 11 cases and was complicated in 2 by subacute bacterial endocarditis. Seven of the 11 cases of rheumatic heart disease did not have hypertension. The size of the heart was determined accurately in 83 cases by means of orthodiagrams and in the remainder was determined by percussion. When only the 83 cases in which orthodiagrams were made are considered, moderate to marked cardiac enlargement was present in 73, and enlargement of slight degree was present in the other 10.*

Objective evidence of cardiac insufficiency, i.e., râles at the lung base, enlargement of the liver, and dependent edema, was found in 82 cases and was more often of moderate than of marked degree. It was probably related to paroxysmal or established auricular fibrillation in 18 of the 82 cases. In the remainder, congestive failure occured with a normal heart rhythm. A diagnosis of endocardial disease was made in 29 of the 143 patients. It was found in 11 of the 19 patients (57.8 per cent) whose systolic blood pressure was below 160 mm. Hg and in only 18 of 124 patients (14.5 per cent) with hypertension. It is noteworthy that aortic valve disease, either alone or combined with mitral lesions, occurred in 27 of the 29 patients who were found to have endocardial disease. Aortic insufficiency alone occurred in 11 patients; pure aortic stenosis in 6; combined aortic stenosis and insufficiency in 5, and aortic disease, either stenosis or insufficiency, was combined with mitral stenosis in 5. The remaining 2 of the 29 patients, both of whom had hypertension, had mitral stenosis.

Seventeen of the 19 nonhypertensive cases had congestive failure, and 11 of the 19 had aortic valvular disease. Of the remaining 8 nonhypertensive cases in which valvular lesions were absent, 3 had angina pectoris and 2 had angina pectoris and coronary thrombosis. Post-mortem examination was done in 1 of these 8 cases and revealed marked left ventricular hypertrophy unexplained by endocardial or pericardial disease. Further, orthodiagrams made on 4 of the remaining 7 cases all showed marked enlargement of the left ventricle. It is, therefore, probable that in these cases, as in the case that came to post-mortem, there had been preexisting hypertension.

POST-MORTEM FINDINGS

A complete post-mortem examination was made in 20 of the 143 cases. The average weight of the heart in 16 cases of hypertension was 587 gm. In 14 of the 16 hypertension cases the heart weighed over 450 gm., and in the remaining 2 the heart weighed 380 and 390 gm., respectively.

*These figures are based upon the assumption that the upper normal limit of the cardiothoracic ratio is 57 per cent[4].

The first of these 2 cases was a female, aged forty years, who had a basophilic adenoma of the pituitary gland, and the second was a male, aged forty-six years, who had chronic nephritis and uremia. In both cases a marked elevation of systolic and diastolic pressures had been repeatedly recorded. In 4 of the 20 cases examined post mortem the blood pressures had been found to be within normal limits while the patients were under observation. The weight of the heart in these four cases was 600, 885, 995, and 640 gm., respectively. The first 2 of these 4 patients had aortic stenosis of sclerotic origin. The third had rheumatic heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, and chronic adhesive pericarditis. In the fourth case no endocardial or pericardial lesion was present which could account for the marked increase in the weight of the heart. In this, as in the other 3 cases, the left ventricle was hypertrophied. Preexistent hypertension was, therefore, likely in this case.

In the 2 cases of hypertension in which the heart weighed less than 400 gm., the left ventricle was moderately hypertrophied and measured 2 cm. in thickness. In the other 18 cases, hypertrophy of the left ventricle was marked, and the increase in the weight of the heart was due to a disproportionate increase in the weight of the left ventricle.

In 2 cases the coronary arteries were normal. In 8 cases the pathological changes in the coronary arteries were restricted to a few macroscopic atheromatous intimal streaks, the lumina of the vessels being widely patent. Five cases showed moderate arteriosclerosis and atheroma, and in 3 these changes were of advanced degree, accompanied by stenosis and calcification of the vessels. Actual occlusion of the artery by thrombus occurred in 2 of the latter cases. In 1 case old organized thrombi were found in the left circumflex and in the right descending coronary arteries; and in the other, a fresh dark red thrombus occluded the right coronary artery at a point of stenosis. In the first instance coronary thrombosis occurred before, and in the second case after, the significant electrocardiograms were taken. The myocardial lesions were variable and were lacking in any semblance of uniformity, and it was noteworthy that in 4 cases there were no demonstrable myocardial changes aside from hypertrophy of individual muscle fibers.

FOLLOW-UP STUDY

A follow-up study of these cases was made in order to determine the possible prognostic significance of these electrocardiographic changes. This study, as has been stated, covers a period of approximately twelve years and includes many recent cases. The duration of life has in all cases been estimated from the date upon which initial electrocardio-

graphic records of the type described were obtained. The cases with normal blood pressure and with hypertension have been dealt with separately.

First, of the 124 patients with hypertension, 20 could not be traced. Of the remaining 104 patients, 61 had died. The duration of life from the time of the first observation in 54 averaged 8.1 months and in the remaining 7, all of whom were known to be dead, the duration of life could not be ascertained. Forty-three patients with hypertension are still living, and at the time of writing the average duration of life of these patients was 17.1 months. The apparent discrepancy in these two average figures for living and dead patients is due to the fact that included with the latter are 4 patients who are still alive three, five and a half, seven, and eight and a half years, respectively, after the electrocardiographic record was obtained. If these 4 patients are excluded, the average duration of life for the living is reduced to 11.6 months.

In the smaller group with normal blood pressure, somewhat similar results were obtained. Of the 19 cases, 7 could not be traced. Eight of the remainder are dead, the average duration of life being 6.6 months. Four are still living, average duration of life being 39.5 months and the maximum being nine and a half years. Thus, of 109 patients accurately traced, 62 are dead; this gives an average mortality of 56.8 per cent in 7.9 months. There is, therefore, no doubt as to the seriousness of the prognosis in patients showing this electrocardiographic abnormality.

SUMMARY

It has been shown that electrocardiograms which exhibit the multiple abnormalities described differ from electrocardiograms of the T_1 type of coronary thrombosis. However, 16 of the 143 patients whose cases were reviewed had coronary thrombosis. In all 16 cases electrocardiograms showed the type of abnormality here recorded, and in none was the changing electrocardiographic picture of myocardial infarction found. Since 14 of these 16 patients had hypertension, the possibility must be kept in mind that antecedent or existing hypertension was the factor responsible for these abnormalities rather than cardiac infarction.

It has been found that arterial hypertension was present in 124 of the 143 patients and that 11 of the remaining 19 patients had aortic valvular disease; from the evidence available preexistent hypertension was probable in at least 5 of the other 8 cases. Thus, in these cases there was present one or other of the two most important factors which determine hypertrophy of the left ventricle. In addition, it was found that left ventricular hypertrophy was present in all cases examined post mortem. It would seem justifiable, therefore, to conclude that these distinctive

electrocardiographic abnormalities were characteristic of certain cases of left ventricular hypertrophy and, since arterial hypertension was by far the most frequent determining cause of that hypertrophy, that these electrocardiographic changes were practically diagnostic of hypertension. Further investigation regarding the relationship of these electrocardiographic abnormalities to left ventricular hypertrophy and to hypertension is in progress and will be reported upon later.*

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*Just before this paper was submitted for publication, a single record of similar electrocardiographic abnormality obtained from a patient with essential hypertension was published by the late Joseph H. Bainton and Julius Burstein, "Illustrative Electrocardiography," New York, 1935, D. Appleton-Century Company.

MORTALITY RATES OF ORGANIC DISEASES OF THE HEART BY GEOGRAPHICAL AREAS IN THE UNITED STATES*

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THE usual practice has been to present crude death rates of organic diseases of the heart by states or other subdivisions of the country, or to present data on the age-specific death rates for a few states or cites. This study was undertaken to determine what differences in mortality, if any, have existed in various ages among a large group of states. It will be seen later that a fair sample from all sections of the United States has been included in the group of thirty-six states studied.

All the data on mortality in this report have been taken from the Mortality Statistics reports of the United States Bureau of Census. Estimates of population have been made from the 1920 and 1930 census reports of the Bureau. The study was limited to the years 1922 to 1929, inclusive, because previous to 1922 deaths after thirty years of age were tabulated differently by age groups. The data for 1930, although available before this study was completed, were not included because doing so would have made little difference in the means of the calculated rates. Only data for states included in the death registration area in 1922 were used. Instead of a presentation of a large number of tabulations for each year for the thirty-six states, the mean or average rate for two four-year periods was used (1922-1925 and 1926-1929). This tended to smooth out fluctuations which were bound to arise from year to year when dealing with small groups of populations, as was the case in certain of the less populated states.

In this study only organic diseases of the heart have been included. In the classification used by the Bureau of Census in the Mortality Statistics reports from 1922 to 1929, deaths from organic diseases are to be found under four headings: (87) pericarditis, (88) endocarditis and myocarditis (acute), (89) agina pectoris, and (90) other diseases of the heart. The total number of deaths for each age listed under the four headings have been used in making the calculations for each group.

The states whose rates are tabulated in Tables I and II have been arranged in groups according to their geographical location, following much the same order which has been used by the Bureau of Census and the United States Public Health Service in various reports. This

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was done in order that a comparison of mortality rates for a whole group of states in the same geographical area might be made with other groups rather than a comparison of single states.

It was impossible to find a suitable standard with which individual states or groups of states could be compared. If the rates were calculated for the entire registration area they were heavily weighted by the large populations and large numbers of deaths from the Northeastern states. If the mean or average of the rates was taken for the thirty-six states, the rates of the states with small populations or those with few deaths caused the result to be low and equally unsatisfactory. It appears that a comparison of one group of states with another is most satisfactory.

It will be noted in Table I that mortality rates per 100,000 population have been tabulated for age groups under thirty years, and in Table II for the groups over thirty years and the crude rate for all ages. In discussing the data contained in these tables the mortality in the younger ages will be considered, then that of the older age groups and the crude rate. By so doing one can consider more readily organic diseases of the heart due to rheumatic and other acute infections among the young, and the degenerative forms which are limited to the older ages. The part that syphilis, also an infectious disease, plays in the mortality of middle life cannot be separated from that of the degenerative forms of heart disease in the data for the white race. Its effects seem somewhat more apparent in the data for the negro.

Numerous surveys have established the fact that rheumatic infections have accounted for most of the cases of organic diseases of the heart in the younger ages (under thirty years). If this assumption is true for all parts of the United States, a study of the mortality in the younger age groups for each state then should give us some indication of the prevalence of rheumatic infections in different sections of the country.

In Table I it is evident that there are certain sections of the United States where mortality rates due to organic diseases of the heart are much higher than others in the younger age groups. Comparatively high rates have prevailed in the states bordering on the Atlantic Coast from Maryland to Massachusetts, in two North Central states and in the Mountain states. The mortality under thirty years of age in these states is consistently above that of other areas. With the exception of the Mountain states this is not surprising.

Although Arizona and New Mexico were not included in the tabulations because they were not in the death registration area until recently, the available data indicate that their mortality for the group under ten years has been slightly under the general average for the

other states in the Rocky Mountain region but equally high for the age groups from ten to twenty-nine years. Why the Mountain states should have a high mortality is not clear, but the consistently high rates of these states seem to be fairly good statistical evidence that this relatively high mortality is of some significance.

It has been shown by a number of observers that rheumatic infections are more common in the northeastern part of the country than

TABLE 1

MORTALITY RATE PER 100,000 POPULATION FOR ORGANIC DISEASES OF THE HEART FOR AGE GROUPS UNDER 30 YEARS, 1922-1925 AND 1926-1929

	UNDER 5		5 – 9		10 – 19		20 – 29	
	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929
New England								
Maine	16.6	19.8	4.9	5.4	11.9	13.2	16.9	15.5
New Hampshire	23.3	11.9	14.6	12.4	13.1	16.7	18.6	15.6
Vermont	12.9	12.6	4.4	6.5	14.7	13.7	15.8	19.8
Massachusetts	20.7	13.5	18.7	14.1	28.9	26.4	29.7	29.3
Rhode Island	25.2	20.3	15.2	12.7	20.4	21.4	25.3	24.9
Connecticut	16.9	15.7	14.9	12.9	20.5	21.9	23.8	26.0
Middle Atlantic								
New York	23.3	17.8	22.2	19.2	35.3	33.8	33.8	34.1
New Jersey	26.2	21.1	22.4	22.0	35.1	30.8	32.3	34.1
Pennsylvania	24.3	23.1	17.9	17.6	29.0	25.1	31.9	34.7
East North Central								
Ohio	14.9	12.4	13.2	10.5	21.3	18.5	25.6	25.2
Indiana	19.2	15.8	12.1	11.4	19.2	17.2	24.7	22.4
Illinois	23.7	21.1	19.8	18.0	25.4	25.4	30.1	31.9
Michigan	22.9	19.4	17.2	14.8	22.1	20.7	25.6	30.8
Wisconsin	13.1	13.1	9.5	10.4	16.5	16.0	19.5	18.5
West North Central								
Minnesota	9.0	7.5	8.7	8.4	16.4	15.0	21.3	20.6
Missouri	10.6	11.1	10.7	10.1	17.3	15.5	23.2	23.8
Nebraska	10.9	13.8	10.6	10.1	16.9	15.4	17.7	16.1
Kansas	14.6	13.3	8.9	5.8	11.2	11.2	17.1	16.8
South Atlantic								
Delaware	24.1	19.5	17.4	19.8	27.1	18.8	24.3	31.1
Maryland*	17.8	13.7	14.9	13.4	22.9	20.0	23.3	24.5
Virginia*	11.3	10.1	7.3	6.4	11.8	10.9	14.1	15.6
North Carolina*	9.9	10.8	5.9	5.3	8.1	10.7	17.7	16.9
South Carolina*	12.5	13.1	5.1	4.5	9.0	7.2	17.5	20.1
Florida*	15.9	10.4	4.4	9.4	8.7	10.7	21.0	24.5
South Central								
Kentucky*	12.3	11.5	5.5	5.9	10.8	9.0	17.2	17.9
Tennessee*	10.0	8.0	4.4	5.5	8.7	9.6	11.9	15.1
Mississippi*	8.1	7.5	3.5	4.6	8.2	6.3	11.1	11.9
Louisiana*	13.3	7.9	3.5	6.3	6.5	6.9	14.8	15.5
Mountain								
Montana	16.8	12.5	16.4	9.0	19.9	22.0	24.5	26.8
Idaho	18.6	14.5	17.7	12.3	20.2	20.9	20.7	23.9
Wyoming	11.8	27.5	18.6	15.5	26.6	21.1	20.4	22.5
Colorado	16.1	21.1	20.0	21.5	29.7	29.7	27.5	27.3
Utah	14.4	18.8	23.5	22.6	43.4	38.5	39.3	36.8
Pacific Coast								
Washington	8.9	7.2	10.5	9.8	18.3	14.8	17.4	19.3
Oregon	15.6	16.9	9.9	8.8	21.3	18.9	20.7	22.9
California	15.7	11.7	12.1	8.0	20.9	17.3	25.1	25.1

*Rates for white race only.

in the Southern states. However, mere geographical location does not appear to be the only important factor in the higher mortality rates, according to the evidence brought out in the present study. In most instances the upper New England states (Maine, New Hampshire, and Vermont) have had a much lower mortality than the other three New England states. The population of the latter differs from the former in that a greater proportion is concentrated in urban centers, a condi-

TABLE II

MORTALITY RATE PER 100,000 POPULATION FOR ORGANIC DISEASES OF THE HEART, OVER 45 YEARS AND FOR ALL AGES, 1922-1925 AND 1926-1929

	30 – 44		45 – 64		OVER 65		ALL AGES	
	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929
New England								
Maine	45.5	43.3	257	287	1954	2200	229	263
New Hampshire	49.9	51.6	292	357	1921	2228	241	291
Vermont	47.4	48.2	300	316	2173	2320	262	277
Massachusetts	68.9	71.5	369	398	2414	2539	235	269
Rhode Island	59.9	66.0	364	397	2140	2533	204	242
Connecticut	59.3	65.1	346	396	2185	2505	199	239
Middle Atlantic								
New York	80.1	83.8	436	485	2598	2931	246	277
New Jersey	80.8	85.7	383	447	2251	2558	206	240
Pennsylvania	73.3	82.5	346	411	2041	2454	187	229
East North Central								
Ohio	56.8	69.1	270	326	1836	2125	177	216
Indiana	41.9	59.5	259	308	1760	2072	187	225
Illinois	71.0	82.7	320	387	1999	2328	186	227
Michigan	61.9	80.0	293	344	2032	2335	183	211
Wisconsin	42.9	49.5	237	267	1736	2056	159	194
West North Central								
Minnesota	46.9	47.8	235	250	1738	1837	144	171
Missouri	54.4	64.9	229	286	1377	1738	145	192
Nebraska	38.1	41.9	210	237	1338	1275	122	158
Kansas	39.1	40.7	189	219	1463	1712	139	168
South Atlantic								
Delaware	65.6	85.1	328	383	1897	2075	201	242
Maryland*	58.3	64.2	316	364	2039	2309	194	229
Virginia*	41.5	41.7	245	271	1832	2146	138	164
North Carolina*	39.2	46 1	212	251	1562	1956	109	128
South Carolina*	47.3	53.5	254	287	1765	2205	112	138
Florida*	50.5	60.7	275	319	1511	1768	149	179
South Central								
Kentucky*	37.2	43.5	177	244	1276	1500	106	129
Tennessee*	31.8	37.5	155	193	1159	1456	88	110
Mississippi*	26.4	34.7	171	200	1264	1568	91	110
Louisiana*	64.2	40.7	295	325	1922	2193	127	147
Mountain								
Montana	44.7	59.6	225	272	1459	1757	105	152
Idaho	39.5	47.7	179	238	1257	1586	92	134
Wyoming	47.7	29.9	221	211	1270	1483	95	110
Colorado	55.0	56.4	225	259	1363	1662	131	166
Utah	72.2	67.4	246	281	1473	1797	123	148
Pacific Coast								
Washington	40.5	45.8	245	268	1561	1912	145	185
Oregon	46.3	48.8	256	279	1651	2003	170	212
California	61.0	60.3	327	342	2109	2273	234	240

*Rates for white race only.

tion which is said to predispose to a greater incidence of rheumatic infections. The question whether a large proportion of foreign-born in a population predisposes to a greater prevalence of rheumatic infections might be raised, but there is no definite evidence on this point to be found in the available data. The effect of crowding, types of housing, and other environment factors would necessarily have to be taken into consideration before claiming that a particular nationality is more or less susceptible to acute rheumatic fever and rheumatic heart disease. However, the fact remains that in Maine, New Hampshire, and Vermont in 1930 the ratio of native white to foreign-born white was approximately 8 to 1 while the ratio for the other New England states was 4 to 1.

In general, the populations of the Middle Atlantic states and Illinois and Michigan show about the same general conditions regarding percentage of urban population and foreign born as is found in the lower New England states. However, the Mountain states present a different picture. On the average only about 37 per cent of the population is classed as urban in contrast to 81 per cent in Massachusetts, Rhode Island, and Connecticut, 78 per cent in the Middle Atlantic states, 71 per cent in Illinois and Michigan, and 55 per cent in Delaware and Maryland. Even among the Mountain states themselves, those with the highest percentage of urban population, namely, Colorado and Utah, have the highest mortality from diseases of the heart. In the Mountain states the proportion of foreign born is much lower than in the East. Climate is another variable which is quite different in the two areas.

In 1930 Viko[1] stated that rheumatic heart disease accounted for a greater percentage of all organic diseases of the heart observed in a clinic whose patients lived in or near Salt Lake City than is the case in some other parts of the country, but he presented no evidence to indicate whether or not rheumatic heart disease is actually more prevalent in that section than elsewhere.

Data for the Southern states and west North Central states in the younger age groups indicate that mortality from organic diseases of the heart is much lower in these regions than in any other sections of the country, a fact which is consistent with the usual conception of rheumatic infections in these areas.

From the data presented it would not be unreasonable to assume that rheumatic diseases of the heart, and probably rheumatic fever also, are about as common in the Mountain as in the Eastern states. If not as common, they probably are more fatal. Studies on the epidemiology of acute rheumatic fever and rheumatic heart disease in the Rocky Mountain area would be of great value in answering these questions.

A slightly different picture is presented for the older age groups, particularly over forty-five years. In general, the states, except for the Mountain states with the higher mortalities in the younger age groups, are ranked in about the same order for the older age groups. In this instance, the mortality for the Mountain states is found to be below that of other areas.

In spite of the fact that the upper New England states have a greater proportion of their population over forty-five years old their death rates are lower than those for the lower New England states in these age groups. Certain southern states show relatively higher rates in the older age groups than in the younger age groups.

Fig. 1 illustrates graphically some of the points previously mentioned. The mortality rates of three geographical areas for each age group in the four-year period from 1926 to 1929 were charted on a semilogarithmic scale. The mean mortality rates for the period appear in the ordinates on a logarithmic scale, and the ages in the abscissae on a uniform scale of years. Such a method will indicate the relative or percentage difference in the rates from one age to another and the relative difference of various groups in the same age. Since the mortality rates show an enormous numerical range from the younger to the older ages, a semilogarithmic chart is more satisfactory because it shows the relative or percentage differences very readily without distortion.

In this chart the similarity of mortality rates in the younger age groups for the Middle Atlantic and the Mountain states is apparent. The Middle Atlantic states were chosen because it has been known that rheumatic fever and organic diseases of the heart have shown a high incidence and mortality in this area for a number of years. Fig. 1 also shows that the percentage difference in the older age groups as compared with the younger is greater for these eastern states than the Mountain states. It also shows the wide difference which exists in the groups under thirty years of age when the mortality of the Southern states is compared with the Northern. However, in the age groups over thirty years the difference in the two areas is less, and the mortality increases with age at approximately the same rate in the South Central area as in the Middle Atlantic.

When considering the crude death rates it is necessary only to point out that the high mortality rate for all ages of the upper New England states covers up the fact that their rates for each age group is generally lower than that of the lower New England states. The reason for this is merely that the population of the former contains a greater percentage of persons over the age of forty-five years, the age when most deaths occur. It is likewise evident that the low crude rate of

the Mountain states covers up the fact that a high mortality exists in the younger age groups. On the other hand, the crude rate of certain southern states masks a relatively higher mortality in the older age groups.

So far the mortality rates of organic diseases of the heart have been considered for the white race only. Crude rates whenever available have indicated that the mortality is greater among negroes than among whites. In the data presented in Table III for the white and colored rates in nine southern states, it is evident that the negro rates are higher in all ages except after 65 years.

The greatest difference in the mortality rates among the two races is to be found in the group from thirty to forty-four years of age, when

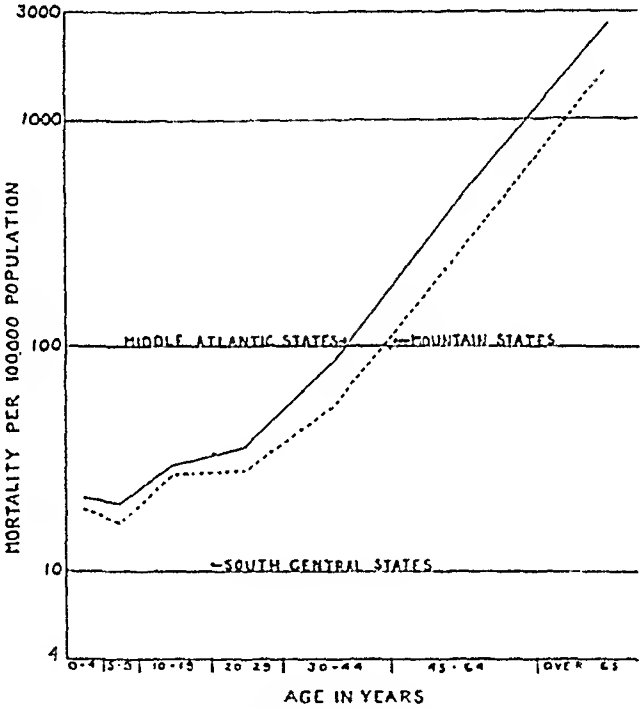

Fig. 1.—Mean mortality rates for organic diseases of the heart by age groups in the Middle Atlantic, Mountain, and South Central states, 1926-1929.

the negro rate is from three to five times that of the white. There is no definite evidence that the greater prevalence of syphilis among negroes accounts for this great difference, but the probabilities are that this is the case.

After sixty-five years of age the mortality of whites is often higher than among negroes. The fact that coronary diseases and certain other types of degenerative forms of heart disease are less frequently reported as the cause of death among negroes no doubt accounts for the fact that the mortality for organic diseases of the heart among negroes is often less than for the white race after the age of sixty-five years.

TABLE III

MORTALITY RATE PER 100,000 POPULATION FOR ORGANIC DISEASES OF THE HEART IN THE WHITE AND NEGRO RACES OF THE SOUTHERN STATES, 1922-1925 AND 1926-1929.

	0-4		5-9		10-19		20-30		30-44		45-64		OVER 65		ALL AGES	
	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929
Florida																
White	15.9	10.4	4.4	9.4	8.7	10.7	21.0	24.5	50.5	60.7	275	319	1511	1768	149	179
Negro	9.0	10.4	9.2	10.3	16.1	18.6	52.5	62.3	168.7	208.4	441	565	1272	1377	146	179
Kentucky																
White	12.3	11.5	5.5	5.9	10.8	9.0	17.2	17.9	37.2	43.5	177	244	1276	1500	106	129
Negro	21.5	19.6	6.6	5.7	26.6	23.8	50.5	58.4	204.1	219.1	635	780	1577	2097	264	325
Louisiana																
White	13.3	7.9	3.5	6.3	6.5	6.9	14.8	15.5	64.2	40.7	295	325	1922	2193	127	147
Negro	10.5	10.8	7.6	10.6	15.4	17.2	53.3	62.3	192.2	219.6	593	714	2021	2444	198	233
Maryland																
White	17.8	13.7	4.9	13.4	22.9	20.0	23.3	24.5	58.3	64.2	316	364	2039	2309	194	229
Negro	33.9	18.0	19.6	12.2	26.0	14.9	48.1	55.5	195.4	228.0	719	800	1990	2191	251	273
Mississippi																
White	8.1	7.5	3.5	4 6	8.2	6.3	11.1	11.9	26.4	34.7	171	200	1264	1568	91	110
Negro	6.7	7.4	7.6	6.3	14.2	11.9	37.9	41.2	106.6	115.0	326	371	1296	1341	118	127
North Carolina																
White	9.9	10.8	5.9	5.3	8.1	10.7	17.7	16.9	39.2	46.1	212	251	1562	1956	109	128
Negro	11.8	10.2	9.9	7.2	16.7	20.6	50.4	56.7	142.9	176.2	444	548	1643	1929	142	165
South Carolina																
White	12.5	13.1	5.1	4.5	9.0	7.2	17.5	20.0	47.3	53.5	254	297	1265	2205	112	138
Negro	10.5	16.2	6.9	7.5	13.6	17.4	71.0	90.4	187.2	256.0	478	674	1620	1786	138	191
Tennessee																
White	10.0	8.0	4.4	5.5	8.7	9.6	11.9	15.1	31.8	37.5	155	193	1159	1456	88	110
Negro	11.6	5.6	6.8	10.3	14.0	18.0	50.5	56.4	165.2	187.4	482	618	1383	1700	177	215
Virginia																
White	11.3	10.1	7.3	6.4	11.8	10.9	14.1	15.6	41.5	41.7	245	271	1832	2146	138	164
Negro	10.6	12.9	8.0	7.2	18.5	18.6	56.4	54.4	211.2	236.0	633	810	1709	2037	203	256

Fig. 2 is a graphic representation of the difference in the white and colored races for the South Central states. All of the Southern states show very much the same picture, i.e., little difference in mortality at the extremes of life and a marked difference in the middle ages.

Although the period of time covered in this study is comparatively short, the mortality has shown some decrease in the younger age groups in certain parts of the country, particularly in the northeastern section. This reduction may be due partly to a decline in the incidence of acute infectious diseases other than rheumatic fever. This is an encouraging sign, even though we have no specific prophylactic meas-

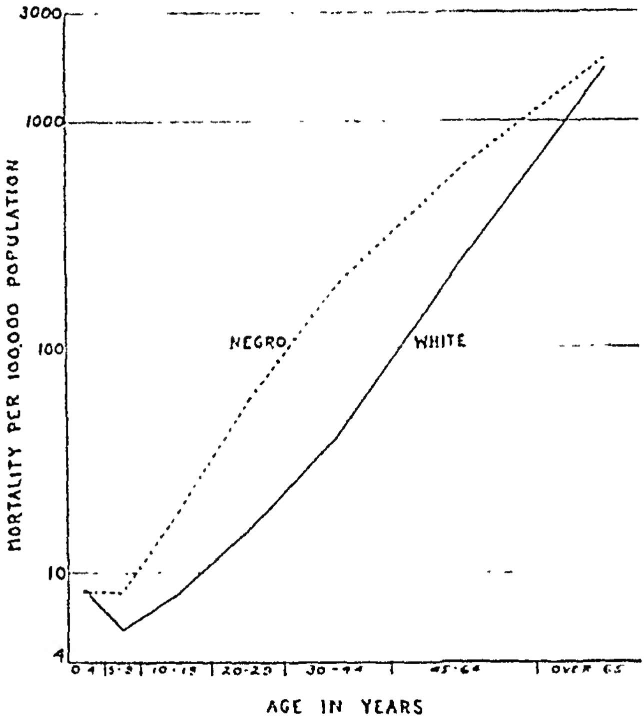

Fig. 2.—Mean mortality rates for organic diseases of the heart by age groups for the white race and negroes in South Central states, 1926-1929.

ures for organic heart disease. In the group over forty-five years, however, a very evident increase in mortality has occurred. More adequate treatment of syphilis in the negro is suggested as one means of preventing many deaths from heart disease in the middle ages of that race.

SUMMARY

Mortality rates for organic diseases of the heart in the younger age groups are high in the Atlantic Coast states from Maryland to Massachusetts, in Illinois and Michigan, and in the Mountain states. The areas with low rates are the west North Central states, and most of the Southern states.

In the older age groups the Northeastern states show the highest mortality. The Mountain area has a relatively low death rate and the Southern states, a higher rate in contrast to the mortality in the younger age groups.

The negro mortality rates in the Southern states for organic diseases of the heart are generally higher than for the white race. The greatest difference is found in the group from thirty to forty-four years of age. It is probably due to a greater incidence of syphilis among negroes.

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A MODIFICATION OF THE WIGGERS-DEAN METHOD OF RECORDING HEART SOUNDS USING AUDIO AMPLIFICATION*

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THE object of this paper is to describe a practical inexpensive method of recording heart sounds that may be used clinically to show the intensity of murmurs and their location in the cardiac cycle.

Many amplifiers for recording heart sounds have been described in the past. A brief review of the history of sound recording has recently been presented by Bierring and his coworkers[1] who also describe a new type of apparatus for recording heart sounds which requires the use of a galvanometer.

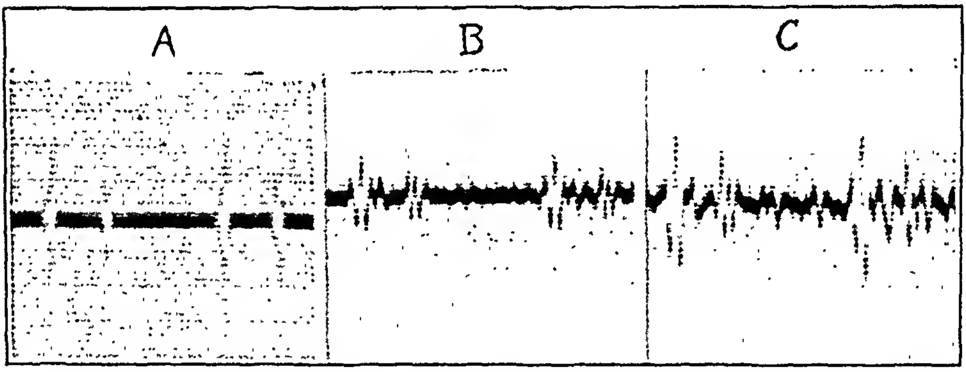

Fig. 1.—Normal heart sounds, recorded from apex: *A*, with crystal microphone method; *B*, with direct Wiggers-Dean method damped; *C*, with direct Wiggers-Dean method undamped.

The method which we have used, utilizes a crystal microphone, the advantages of which have been described elsewhere by Sacks and Marquis.[2] A three-stage audio amplifier, which measures 7.5 inches in height, 8 inches in width, and 9 inches in length complete with batteries, was designed and built by one of us (H. M.) for use with the microphone. For recording, an output receiver from the amplifier is connected with a Wiggers-Dean heart sound segment capsule.[3] This method differs from the direct Wiggers-Dean method in that amplified filtered sounds excite the membrane of the segment capsule instead of unamplified sounds picked up directly from the chest. No damping is used with the microphone method as damping introduces extraneous oscillations in the base line.

*From the Heart Station, Michael Reese Hospital, Chicago.

The time values of the heart cycle are set either by recording Lead II of the electrocardiogram simultaneously with the heart sounds or by using the optically recorded carotid or subclavian arterial pulse tracing (Wiggers[4]). The camera is speeded up in order to spread out the sound tracing and make the interpretation easier.

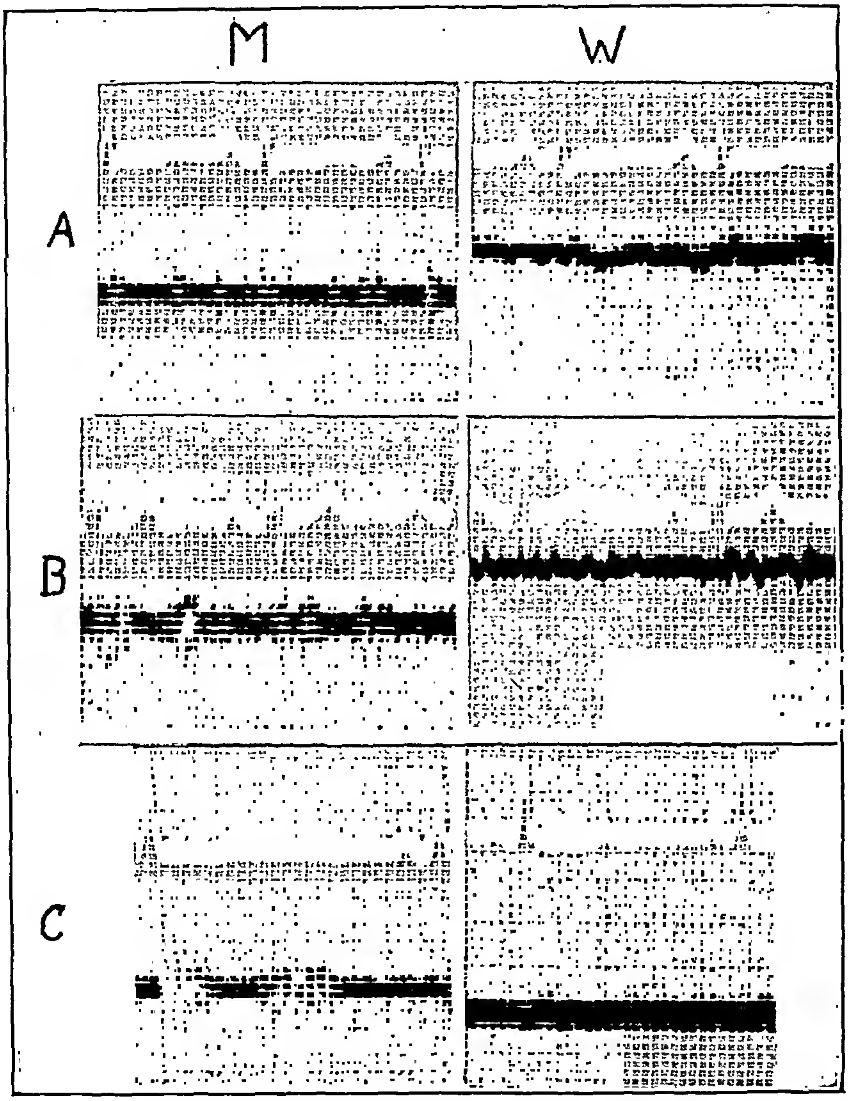

Fig. 2.—Records *M*—heart sounds taken with microphone amplifier method; records *W*—with direct Wiggers-Dean method on the same patient; in both the heart sounds were recorded simultaneously with Lead II. *A*, record of sounds from aortic area, showing diastolic murmur. Clinical diagnosis was rheumatic heart disease, aortic insufficiency. *B*, record of sounds from aortic area, showing systolic and diastolic murmurs, in case of syphilitic heart disease, with an aortic aneurysm. *C*, record of sounds from aortic area records, showing definite diastolic murmur in a case of syphilitic heart disease with clinical findings of aortic valve insufficiency.

The direct Wiggers-Dean method of recording heart sounds usually gives good results with careful technic in appropriate subjects. But when the sounds are distant as in emphysema and obesity[3] and in dyspneic patients, satisfactory tracings have been difficult to obtain. It

is also difficult to record sounds from the base of the heart, and certain murmurs may be missed. Margolies and Wolferth[5] have called attention to the limitations of the direct Wiggers-Dean method in the recording of high-pitched sounds and have utilized an audio amplifying system with the Wiggers-Dean capsule method to overcome this difficulty. These difficulties in recording are also overcome to a large extent with the amplifier system we employed.

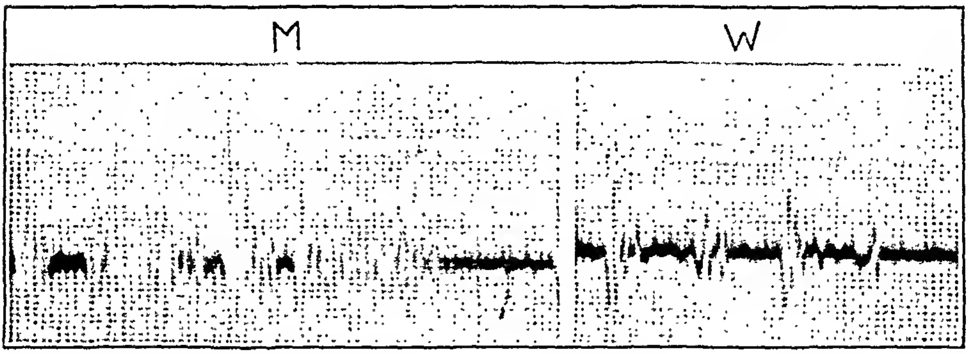

Fig. 3.—Records of heart sounds together with Lead II of electrocardiogram obtained from apex in a case of rheumatic heart disease and auricular fibrillation, showing systolic and diastolic murmurs. Record *M*, taken with microphone amplifier method. Record *W*, taken with direct Wiggers-Dean method.

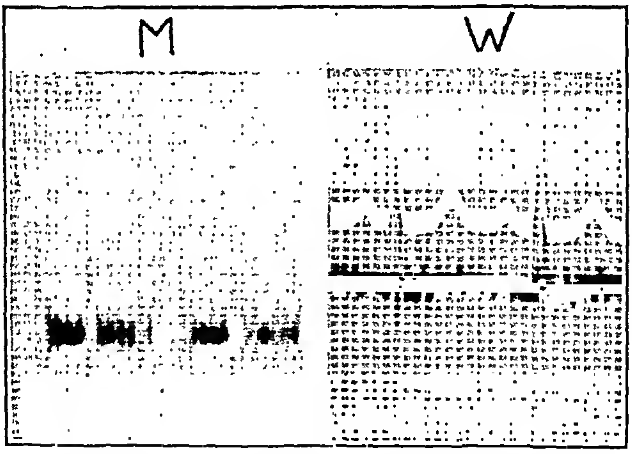

Fig. 4.—Records of heart sound together with Lead II of electrocardiogram obtained from apex in a case of rheumatic heart disease, showing systolic and diastolic murmurs. Record *M*, taken with microphone amplifier method. Record *W*, taken with direct Wiggers-Dean method.

Clinical use of the crystal microphone amplifier apparatus has produced satisfactory records from the apex and base of the heart (Figs. 1, 2, 3, and 4). In all patients tested, distant heart sounds and murmurs, including the soft diastolic aortic murmurs, were recorded satisfactorily, even when the direct method was inadequate. All tracings were free from extraneous vibrations, and the localization in the cycle of normal and abnormal cardiac sounds presented no difficulties.

A "tone control" has been introduced into the circuit, which was found to be valuable in estimating roughly the vibration frequency range of the murmurs.

SUMMARY

A method of recording heart sounds, which uses the crystal microphone with an audio amplifier system, together with the Wiggers-Dean sound segment capsule is described. This method was found satisfactory for clinical use and was found to avoid many of the difficulties present in the direct Wiggers-Dean technic.

The authors wish to acknowledge their indebtedness to Dr. L. N. Katz for his valuable advice and criticisms in developing this method.

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Department of Clinical Reports

AN EXTRAORDINARY DEGREE OF PARTIAL HEART-BLOCK

Report of a Case in Which the P-R Interval Exceeded the R-R Interval*

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Delay in auriculoventricular conduction is a relatively common sign of myocardial involvement, whether caused by inflammatory changes in the conducting tissues as in rheumatic fever or by nutritional disturbances as in coronary sclerosis. High grades of A-V block, i.e., P-R intervals of more than 0.40 sec., are seldom encountered, however, on account of two limiting factors. In the first place, with the higher grades of heart-block the refractory period of the A-V node tends to be so prolonged that impulses become completely blocked there, producing "dropped beats" or a regular two to one or even lower ratio of ventricular response. The second limiting factor is the inherent rhythmicity of the ventricular pacemaker which causes it to "escape" if the impulse from the supraventricular pacemaker is delayed too long. The case here recorded is remarkable in that the ventricle remained dependent on the sino-auricular pacemaker in spite of the fact that the A-V conduction interval was on occasions so long that a second auricular systole had taken place before the impulse from the first auricular systole had reached the ventricle.

The patient (Hosp. No. 645597) was an unemployed laborer who was first admitted to the Second Medical Service of the Boston City Hospital on Aug. 1, 1931, complaining of precordial pain, dyspnea, and episodes of amnesia. He was fifty-six years old at the time.

His family history revealed that his father had died at seventy of apoplexy, and his mother had died at sixty-seven from an unknown cause. His wife had died of "tuberculosis of the stomach" many years before, leaving two healthy children.

At the age of eight years he had had diphtheria, requiring tracheotomy. He had had gonorrhea in his youth and a typical attack of rheumatic fever at thirty-three years. At thirty-seven he passed an examination for life insurance. On account of repeated sore throats, a tonsillectomy was performed at the age of forty-nine years. He had served three enlistments in the Navy following the Spanish-American War and worked at various odd jobs thereafter.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Early in 1926 he began to suffer from shortness of breath, swelling of the ankles, and "skipping of the heart." On Mar. 15, 1926, during a period of marked "skipping of the heart," he suddenly lost the power of speech and then became unconscious. He was brought to the Chelsea Naval Hospital where he gradually emerged from his coma over a period of several days. A residual right facial weakness and aphasia slowly cleared up during his seven months' stay in that hospital. On admission to the Naval Hospital it was noted that the heart rhythm was regular except for occasional dropped beats and that the heart sounds varied in intensity. Pulsus alternans was present to a striking degree, the systolic blood pressure alternating between 112 and 130 mm. Hg and the diastolic between 60 and 70 mm. Hg. There were no signs of congestive failure. The urine showed a slight trace of albumin, and the nonprotein nitrogen in the blood was 56 mg. per 100 c.c. Before his discharge from the hospital the systolic blood pressure had risen to a level of 170-180 mm. Hg and the diastolic to 96-104 mm. Hg, the alternation persisting. The nonprotein nitrogen in the blood fell to 33 mg. per 100 c.c.

His next hospital admission was to the Third Medical Service of the Boston City Hospital on Mar. 8, 1927, on account of a pulmonary embolism from which he made an uneventful recovery. The pulse rate at this time was slow, varying between 40 and 60 beats per minute.

During the year 1931 he suffered from increasing dyspnea and precordial pain and had three amnesic episodes preceded by severe headache and vertigo, lasting for seven or eight hours. These episodes were followed by temporary aphasia. His memory for recent events became poor. He was admitted to the Second Medical Service of the Boston City Hospital on Aug. 1, 1931. Physical examination at that time showed an obese, florid man with a slight residual facial paralysis on the right. There was moderate peripheral arteriosclerosis. The heart sounds were distant, slow and regular except for occasional brief accelerations. There was a systolic murmur at the apex. The chest was emphysematous. There were varicose veins with eczema but no edema of both lower legs. The tendon reflexes were all hypoactive. During his stay of five weeks in the hospital, the pulse rate varied between 45 and 70 beats per minute and the blood pressure between 140 and 160 mm. Hg systolic and 85 to 100 mm. Hg diastolic. The blood Kahn reaction, the urine, and the blood cytology were all normal.

He was discharged from the hospital improved but remained a cardiac invalid with angina decubitus. In January, 1933, he developed a particularly severe attack of precordial pain radiating down both arms and lasting for eighteen hours, unrelieved by nitroglycerine. On readmission to the hospital a week later he was orthopneic and showed coarse râles at the base of the right lung. There was a leucocytosis of 11,000 per c.mm. which persisted for four weeks. He remained in the hospital for five months and was again discharged improved.

Four weeks later, however, he was brought to the hospital for the last time. The oral temperature was 97° F., the pulse rate, 100, and the respiratory rate, 30 per minute. There was some cyanosis of the lips. The heart appeared enlarged; the sounds were distant and regular. The lungs were clear. The blood pressure was 165 mm. Hg systolic and 85 mm. Hg diastolic. There was a persistent leucocytosis of from 14,700 to 20,500 per c.mm. of blood. The hemoglobin was 116 per cent. The nonprotein nitrogen in the blood was 42 mg. per 100 c.c. A teleroentgenogram of the heart showed marked enlargement of the heart and great vessels. He continued to suffer from frequent attacks of dyspnea, cyanosis, and substernal pain, and in one of these attacks he died on July 7, 1933. His treatment during his several hospital admissions consisted largely of rest and sedation, digitalis having been given only once for a brief period at the time of his first admission to the

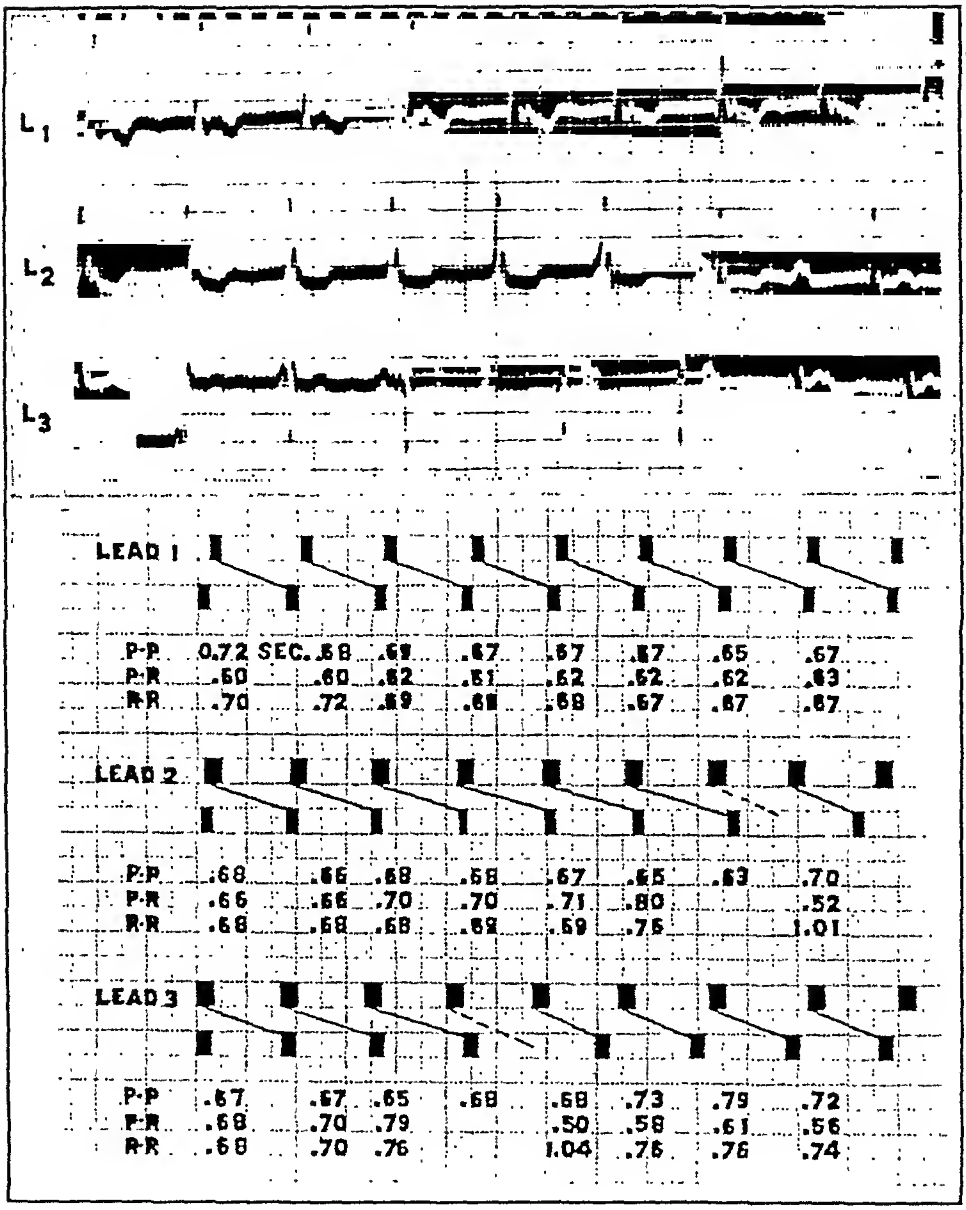

Fig. 1.—*Above*, electrocardiogram taken Jan. 18, 1933, patient B. S., aged fifty-eight years.

Below, diagrammatic representation of same record. The upper line of blocks in each series represents auricular contraction; the lower line represents ventricular contractions; and the connecting lines between them, the conduction intervals. The heavy lines on the background are spaced to indicate intervals of 0.20 sec. and the light lines to indicate 0.04 sec. In Lead I the P-waves are superimposed on initial part of the T-wave and latter part of the R-waves. In Lead II the P-waves are buried further back in the R-waves at the beginning of the record and may be seen to emerge before the preceding R-waves at the fifth and sixth ventricular complexes. The seventh auricular contraction results in a dropped beat. In Lead III the P-wave of the auricular contraction controlling the fourth ventricular contraction may be seen emerging before the third ventricular complex. The next auricular contraction results in a dropped beat. The P-R interval exceeds the R-R interval on five occasions on this record.

Boston City Hospital. The pertinent clinical diagnoses were: arteriosclerosis; coronary sclerosis; coronary thrombosis, old and recent; and partial heart-block.

A total of seventeen electrocardiograms were taken between 1926 and 1933. Through the kindness of Dr. David Ferguson, I was permitted to examine the records taken at the Chelsea Naval Hospital. Most of the records showed a high degree of partial heart-block with P-R intervals ranging from 0.36 sec. to 0.84 sec. As early as Apr. 1, 1926, a record showed P-R intervals of 0.72 sec. On two occasions, once in 1926 and again in 1931, complete heart-block was recorded. Other changes in the electrocardiogram developed during the period of observation. Notching and widening of the QRS complexes appeared and the axis shifted to the left. A deep Q-wave and inverted T-wave appeared in Lead III in 1931, only to disappear the following year as inverted T-waves began to appear in Leads I and II. No significant changes occurred in the electrocardiogram following the record illustrated in Fig. 1. In both Leads II and III of Fig. 1 examples of P-R intervals exceeding R-R intervals may be seen. A diagrammatic sketch of the sequence of events in the electrocardiogram is shown below the tracing.

Autopsy was performed twenty-six hours post mortem by Dr. John Hayes. The significant findings were as follows: There was pitting edema of the legs up to the hips, but the lower edge of the liver was at the costal margin, and there was no free fluid in the serous cavities.

The heart was enlarged, weighing 740 gm. The left ventricular cavity was markedly dilated and contained, attached to the intraventricular septum, a partially organized thrombus measuring 4 by 2.5 cm. The right ventricle was also dilated. The myocardium was reddish brown in color, firm, and showed no gross evidence of fibrosis. The thickness of the left ventricle was 1.4 cm., and of the right ventricle 0.6 cm. There was marked atheromatous degeneration of the coronary arteries, aorta, and aortic cusps.

The lungs showed multiple areas of infarction. The liver weighed 1,900 gm. and the lobules of the liver stood out prominently from its cut surface.

The kidneys were small and finely granular, and the right kidney contained an old infarct.

The anatomical diagnoses (from the gross examination) were: hypertensive heart disease, pulmonary infarction, mural thrombus, cardiac hypertrophy, infarct of the kidney, benign nephrosclerosis, marked chronic passive congestion of the liver, and marked atheromatous degeneration of the coronary arteries and aorta.

Microscopical examination of the heart showed marked deposit of cholesterin beneath the intima of the coronary arteries. The myocardium exhibited a moderate degree of fibrosis which became marked in the papillary muscle where relatively large areas of the muscle cells were destroyed. The small papillary muscle was surrounded by a partially organized thrombus and showed subendocardial fibrosis with early necrosis and a monocytic infiltration of the central portion. Four sections were taken from the intraventricular system. The bundle of His or its branches could not be positively identified in any of these. There was fibrosis in this region, and the muscle fibers showed a tendency to stain poorly or to take an acid stain, with pyknotic nuclei. Such changes were most marked just beneath the endocardium.

The liver showed marked distention of the central sinusoids with erythrocytes while the adjacent liver cells stained poorly with the acid stain and were being infiltrated by polymorphonuclear leucocytes and monocytes. The kidneys showed marked fibrous thickening of the intima of the small arteries with focal areas in which tubules and glomeruli stained more or less homogeneously with acid stain, showing little structural differentiation. Adjacent glomeruli were fibrosed or stained

poorly, with marked thickening of the interstitial fibrous tissue. The lumina of one of the larger and several of the smaller arteries were filled with loose fibrous tissue containing one or two small canaliculizing vessels.

The microscopical diagnoses were: marked atheromatous degeneration of the coronary arteries, moderate perivascular fibrosis of the myocardium, mural thrombus (left ventricle), pulmonary infarcts, hemorrhagic central necrosis of the liver, old infarct of the kidney, and advanced atheromatous degeneration of the aorta.

DISCUSSION

This case is comparable, with regard to the length of the P-R interval, to that reported in 1915 by the late Dr. W. S. Thayer.[1] Dr. Thayer's case was that of a woman fifty-five years old who suffered from extreme bradycardia with occasional syncopal and eclamptic attacks. The pulse rate averaged about 30 per minute. The P-R interval in the electrocardiogram was often more than 0.7 second, and on one occasion it reached 0.88 second. In polygraphic tracings the a-c interval amounted to 0.7 to 1 second. These appear to be the longest recorded A-V conduction times on record. The feature which makes the case here reported unique is that, in spite of an extraordinary delay in conduction, the sinus rate was usually normal or increased so that the P-R interval approximated, and on occasions actually exceeded, the R-R interval. It is noteworthy also that under these circumstances variation in intensity of the first sound of the heart was noted comparable to that observed in complete heart-block and attributable to the same cause, i.e., occasional synchronous contraction of auricle and ventricle.

SUMMARY

A case of extreme degree of partial heart-block is reported on which observations were made over a period of seven years. The P-R interval on one occasion reached 0.80 second, actually exceeding the R-R interval.

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PATENT DUCTUS ARTERIOSUS COMPLICATED BY ENDOCARDITIS AND HEMORRHAGIC NEPHRITIS*

A Case Report

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San Francisco, Calif.,

PULMONARY endarteritis and endocarditis are well known as complications of patent ductus arteriosus. Several adequate reviews are in existence.[1] Since Blumer and McAlenney's discussion, which included twenty-two cases from the literature and six original cases, five additional instances have been reported.[2] These, together with the case here set forth, bring the total of reported cases to 34.

The present case was thought worthy of record because it was closely followed through its entire course; an acute hemorrhagic nephritis developed under observation; and detailed post-mortem studies were possible.

CASE REPORT

M. D., an American schoolgirl, aged eighteen years, was admitted to the medical service of Lane Hospital on July 13, 1931, complaining of fever and weakness for three weeks.

In early childhood a congenital heart lesion had been discovered, and she had never been allowed strenuous exertion. Her health had been excellent, however, and she said she was a "good walker." There was no history of rheumatic infection. Tonsillectomy had been performed at the age of seven years.

About three weeks before entry she began to feel bad on awakening in the morning, to have vague abdominal pains, and to notice weakness and anorexia. She was found to have afternoon fever, sometimes as high as 39.5° C. Because the fever and symptoms persisted, she entered the hospital.

Examination revealed a pale, thin girl, who did not look ill. The temperature was 38.3° C. (rectal); the pulse, 116; respirations, 20; blood pressure, 124/74 mm. No petechiae or evidences of peripheral emboli were found. There was no cyanosis. The tonsillar fossae were clean. The neck veins were not distended. A systolic thrill was palpable, strongest at the pulmonic area, but also present along the entire left sternal border. A suggestion of a diastolic thrill was felt over the pulmonic area. The heart seemed slightly enlarged. The sounds were normal, and the pulmonic second was well defined. There was a continuous "machinery" murmur at the pulmonic area, with both systolic and diastolic accentuation, becoming faintest at the end of diastole. The murmur was transmitted to a certain extent over the whole precordium.

The lungs were clear; the liver and spleen, not palpable. The fingers were not clubbed.

The hemoglobin was 76 per cent (Sahli), the erythrocytes, 4.2 millions; the leucocytes, 11,800 (81 per cent polymorphonuclears). The blood Wassermann reaction was negative. The urine was normal. Roentgenograms revealed slight cardiac

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enlargement with prominence of the left auricle and pulmonary conus. An electrocardiogram showed sinus tachycardia. Two blood cultures yielded *Streptococcus viridans.*

The diagnosis was made of congenital heart lesion (patent ductus arteriosus) and subacute bacterial endocarditis.

As the temperature subsided in a few days, the patient was dismissed with instructions to remain in bed. Subsequent care took place for the most part at her home. There were in all eleven hospital admissions, most of them of one or two days' duration for the purpose of blood transfusion.

Course.—For several months she seemed to hold her own before beginning a gradual decline, which became rapid in the final month. Her spirit, however, was high, and her will to get well strong until the very end.

There was almost constant septic fever, increasing as her condition grew worse. Daily temperature variations of as much as 5° C. were not uncommon in the later months. On one occasion the rectal temperature swung from 36.0° to 42.1° C., and back again within twenty-eight hours.

Death took place on July 8, 1932, a little more than a year after the onset of illness.

The only specific therapy attempted was a course of seven subcutaneous injections of autogenous vaccine, which had no apparent effect. She received a total of twenty blood transfusions as treatment both for the infection and for the anemia which developed rapidly in spite of vigorous iron therapy.

Beginning three months after the onset of the present illness, she had frequent attacks of chest pain with bloody sputum. These were thought to be due to pulmonary infarcts, although no physical signs of infarction could ever be elicited. A few attacks were followed by pleural effusions which did not require drainage. At no time were there any evidences of embolism in the peripheral circulation, although they were constantly looked for.

In April, 1932, nine months after the onset of the endocarditis, the spleen became palpable for the first time. At about the same time the fingers began to show clubbing. During the last months of illness the heart murmurs increased markedly in intensity without change in their character. The pulse never became rapid disproportionately to the temperature.

Blood.—The blood counts are detailed in Table I. It will be noted that the blood count was practically normal at onset but that anemia developed within two months. The series of twenty transfusions, each consisting of 500 c.c. of citrated blood, which were given in the ensuing nine months, were successful until the very end in preventing the anemia from becoming profound.

The results of the blood cultures are shown on Table II. Until the terminal flooding of the blood stream with organisms, the colonies in poured agar plates were small and appeared only after several days, even under partially anaerobic conditions.

Roentgenograms of the chest were repeated in October and again in April. In the first of these the cardiac enlargement was greater than it had been in July, and there was an extraordinary change in the size and shape of the heart shadow when the patient changed her position. This change was never satisfactorily explained and later ceased to occur. In April, the cardiac silhouetté was still further enlarged. Many scattered, rather dense shadows not previously present were seen throughout the lung fields. These were interpreted as the remnants of infarcts.

Urine.—The urine remained perfectly normal until February (seven months after onset). In September, a faint trace of albumin was found at one examination, and an Addis concentration test was performed. This yielded the following results, all of which are within normal limts for twelve-hour excretion.

TABLE I

BLOOD COUNTS

DATE	HG. PER CENT (S.)	R.B.C. MILLIONS	W.B.C.	POLYS PER CENT	PLATELETS	RET. PER CENT
7/13/31	76	4.2	11,800	76		
9/19/31	55	3.8	20,400	85		
9/24/31			Transfusion I			
9/27/31	85	4.8	14,800	78		
9/28/31			Transfusion II			
10/ 1/31			Transfusion III			
10/ 5/31	95	5.4	12,200	81		
10/ 6/31			Transfusion IV			
10/ 7/31	95	5.4	----	--		
10/12/31			Transfusion V			
10/12/31	95	5.6	----	--		
10/20/31	92	4.9	10,800	69		
10/26/31	93	5.0	----	--		
11/ 1/31	88	4.7	10,800	52		
11/ 5/31	79	4.4	13,200	55	397,700	7.0
11/ 6/31			Transfusion VI			
11/ 7/31	97	5.4	11,100	73		
11/19/31	87	5.0	8,800	57		
12/ 1/31	77	3.7	7,700	--		
12/ 7/31	77	4.0	17,200	74		
12/ 7/31			Transfusion VII			
12/ 8/31	93	5.3	----	--		
12/18/31	86	5.0	13,200	77		
1/15/32	75	3.8	13,200	75		
1/15/32			Transfusion VIII			
1/16/32	86	5.1	----	--		
2/ 5/32	79	4.0	12,500	65		
2/26/32	58	3.6	11,600	81		
2/26/32			Transfusion IX			
3/16/32	59	3.3	22,800	72		
3/19/32			Transfusion X			
3/21/32	73	3.8	20,300	86		
3/21/32			Transfusion XI			
3/22/32	87	4.8	----	--		
3/26/32	81	4.1	11,000	72		
4/ 8/32	56	3.1	12,400	82		
4/ 9/32			Transfusion XII			
4/22/32	50	3.9	12,400	80		
4/22/32			Transfusion XIII			
4/23/32	60	4.1	14,000	73		
4/28/32			Transfusion XIV			
4/28/32	60	4.0	14,600	82		
5/ 6/32	58	3.6	15,000	85		

TABLE I—CONT'D

DATE	HG. PER CENT (S.)	R.B.C. MILLIONS	W.B.C.	POLYS PER CENT	PLATELETS	RET. PER CENT
5/ 6/32			Transfusion XV			
5/ 9/32	65	4.1	15,000	79		
5/11/32			Transfusion XVI			
5/11/32	72	4.1	----	--		
5/16/32	72	3.9	18,200	79		
5/23/32	55	3.6	17,800	62		
5/24/32			Transfusion XVII			
5/24/32	65	4.1	13,600	68		
5/28/32	60	3.8	25,400	69		
5/31/32			Transfusion XVIII			
5/31/32	69	4.1	------	--		
6/ 4/32			Transfusion XIX			
6/ 5/32	75	4.5	------	--		
6/ 6/32	77	4.7	23,200	88		
6/ 7/32	--	2.3	23,100	83		
6/ 7/32			Transfusion XX			
6/ 7/32	45	3.4	25,800	78	104,700	18.2

TABLE II

BLOOD CULTURES

DATE	GROWTH IN BROTH	PLATES COL. PER C.C. BLOOD
7/15/31	++	+
7/17/31	++	+
9/21/31	+	17
10/ 4/31	+	0
10/18/31	+	?
11/ 1/31	+	0
1/15/32	+	0
2/26/32	+	5
3/22/32	+	2
4/ 9/32	+	16
4/22/32	+	10
5/20/32	+	?
7/ 7/32	+++	830

Volume—102 c.c.
Specific gravity—1.032
Protein—7.4 mg.
Casts—5,600 (100 per cent hyaline)
Red blood cells—none seen
White and epithelial cells—1,500,000

In February, albumin, casts, red cells, and white cells began to make their appearance in voided specimens. A concentration test was obtained in May, with the following twelve-hour values:

Volume—220 c.c.
Specific gravity—1.015

Protein—570 mg.
Casts—1,300,000
Red blood cell casts—20 per cent
Epithelial casts—68 per cent
Granular casts—12 per cent
Red blood cells—106,000,000
White and epithelial cells—260,000,000

These figures Dr. Addis interpreted as indicating an active hemorrhagic nephritis with marked degeneration of the tubules.

In June, edema of the ankles, soft and pitting, made its appearance. On salt restriction this diminished temporarily, but progressed within a few weeks to a generalized anasarca. At her final admission in July, the urine boiled solid and was loaded with formed elements, but the blood urea was only 45 mg. per 100 c.c. of blood.

Mode of Death.—During the final month, while the edema was spreading, she appeared to lose ground rapidly. She lost her appetite, became fretful, and was racked by cough productive of pinkish watery sputum, apparently the result of mild pulmonary edema. A few days before death, purpura appeared over the antecubital fossae. This became confluent and spread over almost the entire body. She gradually became lethargic and cold, and finally ceased breathing, apparently the victim of bacterial toxemia rather than of cardiac or renal failure.

Post-Mortem Examination.—The body was that of a slender girl about nineteen years old. The body was warm, rigor mortis absent. The pupils were dilated and equal. The conjunctivae were pale and clear. The skin and mucous membranes showed a marked pallor. Numerous petechial hemorrhages and extensive areas of purpura were present over the lateral aspects of each arm and upper portion of the forearm. A few small petechiae were scattered over the right thigh and left leg. Small hemorrhagic spots were present in the adventitia at the base of the aorta, in the epicardium over the right auricular appendage, and at the base of the pulmonary artery. A diffuse purpuric infiltration was present in the gastric mucosa and in the bladder. Small purpuric areas were present in the cecum.

A moderate pitting edema of both extremities was present. The subcutaneous tissues over the thorax and abdomen also showed moderate edema.

The peritoneum was smooth, glistening, and contained approximately 400 c.c. of thin, slightly turbid, blood-tinged fluid. The pleurae were free of fluid. The pericardial sac contained 200 c.c. of clear, straw-colored fluid.

The left lung showed no scar at the apex. Both lobes contained numerous infarcts, varying in size from 1 to 3 cm. in diameter. Some were partially organized, others were of recent origin. The right lung showed a scar at the apex. Throughout all three lobes numerous infarcts of various size and age were present. The bronchi contained a small amount of frothy, blood-tinged mucus. The peribronchial and peritracheal nodes were moderately enlarged and edematous. The spleen was moderately enlarged, measuring 16 by 11 by 8 cm. The capsule was smooth and bluish brown in color. On cut section the malpighian bodies were prominent, and the pulp was firm and of a dark, reddish brown color.

The heart appeared about twice normal size. Both right and left ventricles were dilated. The ventricular muscle was of normal thickness, rather pale and flabby. The right ventricular wall measured 3 mm. in thickness, the left 10 mm. in thickness. Mural vegetation measuring 1.5 by 1 by 0.8 cm. was present on the endocardium of the right ventricle, 6 cm. from the pulmonary valve, and near the insertions of the chordae tendineae of the tricuspid valve. All the valves were normal except the pulmonary. The pulmonary ring measured 7 cm. in circumference. The leaflets were completely destroyed except at the bases where they were thin and delicate. Extending from a point just beneath the valve and into the pulmonary artery for

a distance of 3 cm., was a cauliflower-like mass of yellowish vegetations which presented a pale greenish tint in addition to the yellow color. Upon opening the valve it appeared as though the orifice was completely occluded by these vegetations. A patent ductus arteriosus was present. The pulmonary end was at a level 5 cm. distal to the base of the pulmonary valve. Projecting outward from the lumen of the ductus was a small polypoid mass of similar yellowish green vegetations measuring 1 by 0.8 by 0.7 cm. A moderate dilatation of the pulmonary artery was present. The lumen of the ductus arteriosus was almost completely occluded by vegetations and measured from 2 to 3 mm. in diameter (see Fig. 1). On the aortic side of the ductus two small polypoid vegetations were present. No calcified plaques were noted in the aorta.

Both kidneys measured 11 by 5 by 3.5 cm. The perirenal tissues showed moderate edema. Both renal capsules stripped rather easily. The renal surfaces were congested, brownish red in color, speckled diffusely by numerous small hemorrhages, pinpoint in size, ranging in color from dark brown to bright red. Between the

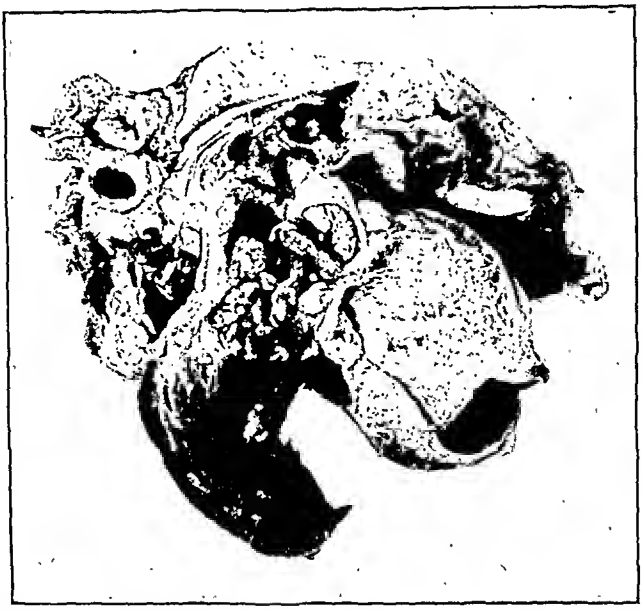

Fig. 1.—Right ventricle of heart. Note the mural vegetation, the cauliflower-like mass of vegetation on the pulmonary valve, and the vegetations on the pulmonic side of the ductus arteriosus. A match is inserted in the orifice of the ductus arteriosus.

hemorrhagic areas numerous small yellowish areas were present. Cut section showed in addition a moderate edema and a moderate cloudy swelling. The mucosa of the renal pelvis was pale, smooth, and glistening.

Histological Examination.—The heart muscle was normal in appearance.

The liver showed a marked congestion throughout. The central sinusoids were considerably widened. The neighboring liver cells were slightly atrophic, contained small amounts of brown granular pigment, and showed a slight fatty degeneration. Some of the periportal areas showed small collections of lymphocytes.

The peribronchial lymph nodes contained a number of large mononuclear phagocytes filled with brown granular pigment in the lymph sinuses.

Sections of the lungs showed infarcts of varying ages. A number of the alveoli were filled with plasma containing scattered numbers of large mononuclear phagocytes.

The skin of the arm showed numerous small hemorrhages into the areolar tissue in the depth of the corium at the level of the coil glands.

The stomach showed a marked congestion of the mucosa and a hemorrhagic infiltration of the superficial portion.

In the kidneys a number of glomeruli showed necrosis of individual capillary loops. Other glomeruli showed an exudation of coagulated material in Bowman's capsule. A few glomeruli showed frank hemorrhage, with numerous blood casts contained in the neighboring tubules. In addition to the above embolic glomerular changes, a number of the glomeruli showed adhesions between the tufts and the neighboring epithelium of Bowman's capsule. A few showed beginning formation of epithelial crescents. The tubules were of varying size, some being small and atrophic. Numerous hyaline, epithelial, and cellular casts were contained therein. Small groups of lymphocytes were scattered throughout the cortex. The arteries appeared essentially normal.

Bacteriological Examination.—The blood culture showed a growth of *Streptococcus viridans,* alpha (Brown).

Anatomical Diagnoses.—The anatomical diagnoses were: open ductus arteriosus; subacute arteritis of the ductus arteriosus; subacute endocarditis of the pulmonary valve; septicemia (*Streptococcus viridans*); embolism of the pulmonary artery with multiple infarcts in the lungs; early subacute nephritis; acute, focal, embolic nephritis; purpura hemorrhagica, and secondary anemia.

DISCUSSION

Two points of especial interest are presented by this case: (1) the infective process at the site of the congenital anomaly and (2) the renal lesion. Adequate discussion of the first of these points is found in the reviews previously cited,[1] and we shall simply point out that here the endocardial lesions were limited to the ductus, the pulmonary artery, the pulmonic valve, and the wall of the right ventricle. In spite of the multiple infarctions of the lungs and the protrusion of vegetations from the ductus into the aorta, no systemic infarctions were found.

The onset of nephritis early in 1932 was not accompanied by clinical signs or symptoms. The patient noted nothing peculiar about the urine, and there was no edema. The sudden onset of edema in June was not accompanied by evidence of renal failure.

Clinically, the renal lesion was a typical active hemorrhagic nephritis. Pathologically, there was present a diffuse glomerulonephritis as well as the focal embolic type of lesion first described by Löhlein[3] and Baehr.[4] The interesting discussion of such lesions by Addis and Oliver[5] cannot be supplemented here.

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Department of Reviews and Abstracts

Selected Abstracts

Segal, Maurice S.: Auricular Fibrillation and Auricular Flutter in the Course of Subacute Bacterial Endocarditis. New England J. Med. **212:** 1077, 1935.

A review of 192 cases of bacterial endocarditis revealed two cases of auricular flutter and three cases of auricular fibrillation in the course of subacute bacterial endocarditis. One case of auricular fibrillation appeared in the course of acute bacterial endocarditis. The case reports with autopsy protocols and additional case reports from the literature are included.

The cases of auricular fibrillation or flutter occurring in the course of active subacute bacterial endocarditis all showed evidence of mitral valve involvement alone or in combination with the aortic valve.

In the cases of fibrillation or flutter, when the mitral valve was involved by the vegetations, there was found either a normal mitral orifice, mitral regurgitation, or moderate mitral stenosis. No cases of severe mitral stenosis were found. The circumferences of the mitral orifices ranged from 9.5 cm. through 15 cm.

Terminal circulatory failure was found in 50 per cent of the cases of auricular fibrillation or flutter in the course of subacute bacterial endocarditis.

The rare incidence of auricular fibrillation in the course of active subacute bacterial endocarditis cannot be attributed entirely to the rare incidence of revere mitral stenosis in this disease.

The integrity of the myocardium and the underlying physiological and biological state would appear to be more closely related to the pathogenesis of auricular fibrillation than the grade of mitral stenosis per se.

Baker, Roger Denio: Endocardial Tuberculosis. Arch. Path. **19:** 611, 1935.

Endocardial tuberculosis is not uncommonly encountered at necropsy, most frequently as a part of generalized miliary or disseminated tuberculosis. Scattered tubercles from microscopical size to a diameter of 3 or 4 mm. may occur in any part of the endocardium, including the valves. They probably arise by implantation through the coronary arteries and directly from the blood of the heart. Rarely they may be polypoid or pedunculated.

Endocardial tuberculosis may also develop from the extension inward of pericardial and myocardial caseous masses, which may ulcerate and produce generalized tuberculosis. With staining for elastic tissue, it can be shown that a myocardial tuberculous process bulging into the cavity of the heart but apparently covered with a smooth endocardial surface is in some cases really invading the endocardium.

A convincing report of tuberculous endocarditis as a diffuse process at the line of closure of the valves, somewhat analogous to rheumatic and pyogenic endocarditis, has occurred in the literature possibly once. In general, however, tuberculosis has no especial affinity for the line of closure and does not produce thrombotic vegetations.

Endocardial tuberculosis may interfere with cardiac function in the rare instances in which caseous nodules involve the valves.

Sclerosis of the endocardium and healed fibrous or calcified valvular lesions noted at autopsy were not shown to be due to the toxic action of a tuberculous process elsewhere in the body.

Bryan, A. Hughes, Evans, William A., Jr., Fulton, Marshall N., and Stead, E. A., Jr.: Diuresis Following the Administration of Salyrgan: Its Effect on the Specific Gravity, the Total Nitrogen and the Colloid Osmotic Pressure of the Plasma of Normal and of Edematous Dogs. Arch. Int. Med. **55:** 735, 1935.

Studies are reported concerning the effect of the diuresis following the administration of salyrgan on the specific gravity and the colloid osmotic pressure of the plasma in normal dogs and on these same factors plus the total nitrogen content of the plasma in dogs made edematous by plasmapheresis and by the feeding of salt and a low protein diet.

When salyrgan alone was administered to normal dogs, the diuretic response was slight and was not accompanied by any significant changes in the plasma specific gravity or in the colloid osmotic pressure.

Following the administration of water by mouth, a fall occurred in the measurements which was not significantly altered when water and salyrgan were administered together.

In edematous dogs salyrgan produced a marked and prolonged diuresis. No significant changes were observed in the specific gravity, the total nitrogen content, or the colloid osmotic pressure of the plasma before the onset of diuresis. Coincident with the diuresis, however, a sustained rise in all of these values occurred.

The findings are discussed in relation to current theories of the action of salyrgan as affording no evidence of an extrarenal action and indicating predominantly a direct effect on the kidney.

Stroud, W. D., Livingston, A. E., Bromer, A. W., VanderVeer, J. B, and Griffith, G. C.: The Use of Verodigen (a Digitalis Glucoside) in Cardiovascular Disease, Its Biological Assay, and Pharmacological Action. Ann. Int. Med. **8:** 710, 1934.

A clinical study of the therapeutic efficiency of verodigen—the gitalin glucoside of digitalis—has been made upon: (a) five patients with established auricular fibrillation and one patient with auricular flutter, previously untreated with digitalis; (b) two patients with regular sinus rhythm and advanced congestive heart failure; (c) fourteen patients with established auricular fibrillation, previously controlled with whole leaf digitalis preparations or digalen.

Verodigen was found to control the ventricular rate in established auricular fibrillation; to produce clinical improvement, with marked diuresis, in patients with congestive heart failure and regular sinus rhythm; and to produce in the electrocardiogram S-T interval and T-wave changes, characteristic of digitalis action.

Careful clinical observation revealed $\frac{1}{240}$ grain of verodigen to be equivalent to one cat unit (approximately $1\frac{1}{2}$ grains of powdered digitalis leaves).

The total dosage necessary for optimum digitalization varied from $\frac{1}{10}$ to $\frac{1}{16}$ grain, administered over a period of five to six days.

The most frequent adequate maintenance dose of verodigen was $\frac{1}{240}$ grain daily.

Toxic effects from overdosage with verodigen were similar to those produced by whole leaf digitalis preparations.

The potency of verodigen demands careful observation in its administration, especially with patients who have recently been taking any digitalis preparations.

Spink, Wesley W.: Cardiovascular Complications of Trichinosis, Arch. Int. Med. 56: 238, 1935.

Acute myocarditis occurring in trichinosis may be a nonspecific inflammatory reaction due to the invasion of the myocardium by larvae.

A review of the literature shows that other cardiovascular manifestations include congestion and hemorrhage of the eyes, lungs and gastrointestinal tract; edema; thrombosis; embolism with infarction; and hypotension.

Six of eighteen cases of trichinosis (33.3 per cent) showed electrocardiographic changes. These changes included an initial flattening or inversion of the T-wave, especially in Lead II, the wave subsequently becoming upright; low amplitude of the QRS complex, and intraventricular block.

The postmortem changes in a fatal case of trichinosis with myocarditis are presented. Another case is recorded in which trichinosis was complicated by a permanent right hemiplegia.

Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient With Concretio Cordis, Arch. Int. Med. 56: 250, 1935.

A case is reported in which a high degree of obstructing pericarditis was present. This pericarditis was due to infection of the pericardium with *Staphylococcus aureus.* Removal of a portion of the pericardium was followed by a fall in venous pressure, a rise in cardiac output and an increase in pulsation of the heart. Increased venous pressure and decreased cardiac output appear to be the chief mechanisms underlying the symptoms and signs of concretio cordis.

Koucky, J. D., and Milles, G.: Stab Wounds of the Heart: A Study of Electrocardiographic Changes, Polyserositis and Pericarditis, Arch. Int. Med. 56: 281, 1935.

A case of stab wound of the heart with recovery is reported.

Complete electrocardiographic studies and their comparison with similar studies show that a Pardee curve, replaced after about ten days by an inversion of the T-wave, occurred in all cases. A complete return to the normal curve is the rule.

Our case was complicated by polyserositis, which may have resulted from the use of surgical solution of chlorinated soda in irrigating the pericardial sac after the development of pericarditis. The mechanism of the development of polyserositis is discussed.

Roentgenographic visualization of the pericardial sac after injection of an iodized and chlorinated peanut oil was carried out. The pictures disclosed little obliteration of the pericardial sac.

The operation performed without anesthesia or anything more than the most cursory attempts at sterility, necessitated by the extreme state of the patient, resulted in ultimate and complete recovery.

Bernstein, Alan: Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, Am. J. M. Sc. 190: 317, 1935.

A fatal case of periarteritis nodosa without peripheral nodules, suspected and proved by biopsy antemortem, is recorded. The patient's illness was characterized by weakness, emaciation, fever, peripheral neuritis, abdominal pain, edema, occlusion of a central retinal artery, deafness, vacillating hypertension, tachycardia, anemia with leucocytosis and eosinophilia, and changes in the urine. The Wassermann reaction was positive. Potassium iodide failed to arrest the progressive course of the disease.

Mention is made of six other cases of periarteritis nodosa in the files of this hospital. One of these was diagnosed at autopsy; a second, at laparotomy. The last four were recognized by searching through the autopsy material of the department of pathology.

The significance of some of the symptoms and signs encountered in periarteritis nodosa is appraised. Reasons are offered to indicate that the disease may not be quite as uncommon as the paucity of recognized cases would lead one to believe.

Krahulik, L., Rosenthal, M., and Loughlin, H. E.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood With Meningeal Involvement, Am. J. M. Sc. **190:** 308, 1935.

1. A case of necrotizing panarteritis (periarteritis nodosa) in a girl, aged nine years, is presented.
2. The widespread vascular lesions correspond to the degenerative, inflammatory and granulation tissue stages of this disease, as described by Arkin.
3. A primary subacute leptomeningitis due to periarteritis nodosa is described. No other cases of primary meningitis either in children or adults have been reported.
4. The occurrence of unusual features, such as gastrointestinal ulceration with perforation and peritonitis, ulceration of the skin following injury, and the occurrence of ocular lesions has been briefly discussed.

Middleton, W. S., and McCarter, J. C.: The Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. **190:** 291, 1935.

From this review of the subject certain deductions regarding periarteritis nodosa seem reasonable:

1. The incidence of the disease probably greatly exceeds its recognition clinically and pathologically.
2. The pathology consists of a necrotizing arteritis, subacute and chronic cellular and fibrinous exudation, aneurysm formation, thrombosis, and fibroblastic proliferation and repair. The smaller arteries and arterioles are affected; and degeneration and infarction in the areas of supply are common.
3. Etiologically periarteritis nodosa is probably closely associated with the "rheumatic group" of diseases.
4. The tetrad of Meyer and Brinkmann, chlorotic marasmus, polyneuritis and polymyositis, striking abdominal manifestations (cramps, vomiting, diarrhea, melena and perforation), and nephritis, offers a logical foundation for the clinical appreciation and diagnosis of periarteritis nodosa.
5. Unexplained fever, polymyositis, polyneuritis, and eosinophilia constitute peculiar grounds for the consideration of this diagnosis.
6. Wherever the question arises, recourse should be had to biopsy of accessible nodules or voluntary muscle.
7. Further study may grant diagnostic values to ophthalmoscopy, electrocardiography, and roentgenography of the lungs in periarteritis nodosa, as yet not clearly established.

Friedman, Ben, Resnik, H. Jr., Calhoun, J. A., and Harrison, T. R.: Effect of Diuretics on the Cardiac Output of Patients With Congestive Heart Failure. Arch. Int. Med. **56:** 341, 1935.

Diuretic drugs, even when administered to patients with minimal edema, often produce marked relief from dyspnea. The vital capacity is frequently increased following their administration.

Constant effects on the cardiac output have not been observed following the administration of these drugs. Occasionally the output is diminished. This effect is believed to be due to loss of peripheral edema, for the blood supply of edematous tissues is, in proportion to their metabolic needs, often relatively greater than the blood supply to the tissues in general. In some instances the cardiac output is increased by diuretic drugs. This effect is believed to be dependent on an action of these drugs on the heart and possibly to be related to loss of edema from the cardiac musculature. In many instances the administration of diuretic drugs is followed by no demonstrable change in the cardiac output. In such instances it is believed that the peripheral and cardiac actions of the drugs tend to neutralize each other. In favorable circumstances diuretic drugs appear to cause benefit both by tending to decrease the load on the heart and by increasing the ability of the heart to carry its load.

The foregoing evidence is interpreted as indicating that diuretic drugs are of more than symptomatic value. They should be employed frequently for ambulatory patients who have minimal edema or who are suspected of having latent edema.

Riseman, J. E. F., Gilligan, D. R., and Blumgart, H. L.: Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland: The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy, Arch. Int. Med. **56:** 38, 1935.

Studies of the sensitivity of the cardiovascular system of man to injections of epinephrine before and after total thyroidectomy are presented.

Three aspects of the physiologic action of epinephrine have been studied: (1) the sensitivity to epinephrine injected intravenously in patients with normal cardiovascular systems, angina pectoris or chronic cardiac failure; (2) the sensitivity to epinephrine of patients with various levels of basal metabolism; and (3) the rôle played by sensitivity to epinephrine in the improvement which occurs following total ablation of the thyroid gland in patients with angina pectoris or chronic heart disease.

Dilute solutions of epinephrine of known concentrations were injected by constant intravenous drip, and the responses of the blood pressure, heart rate, respiratory rate and depth, consumption of oxygen, and blood sugar content were measured. Eighty-six studies were made in seventeen subjects.

The intravenous administration of epinephrine was followed by a definite and characteristic increase in the systolic blood pressure, heart rate, consumption of oxygen of the body, rate and depth of respiration, and blood sugar content. The changes in diastolic blood pressure were variable and not great.

The responses to a given amount of epinephrine injected intravenously were strikingly similar when repeated measurements were made in a given subject under controlled conditions. The responses varied from person to person.

The response of the systolic blood pressure was closely related to the rate of injection of epinephrine and was found to be the most valuable single index of the patient's sensitivity to epinephrine. The changes in heart rate, diastolic blood pressure, consumption of oxygen, and measurements of respiration were not as directly related to the dose of epinephrine. Patients with angina pectoris and those with congestive heart failure were not more sensitive to epinephrine than patients with no evidences of cardiovascular pathologic changes.

The sensitivity to epinephrine as measured by the aforementioned generally accepted indices remained unchanged after total thyroidectomy so long as the basal metabolic rate was not lower than minus 30 per cent and the patient was free from distressing symptoms of myxedema.

When marked myxedema developed and the basal metabolic rate decreased below minus 30 per cent, a decreased response of the blood pressure and the heart rate to epinephrine became manifest in some instances.

The results of the present investigation show that the clinical improvement which followed total ablation of the normal thyroid gland is independent of any changes in the sensitivity to epinephrine, no alteration in the response to epinephrine being evident at the levels of hyperthyroidism maintained in our patients after operation.

Observations are presented which provide additional evidence that the relief from pain experienced by patients with angina pectoris immediately after total thyroidectomy, when there is no change in the basal metabolic rate or in sensitivity to epinephrine, is due to the interruption of sensory impulses from the heart to the central nervous system.

Duff, G. L.: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. *20: 259, 1935.*

Arterial lesions which resemble those of human arteriosclerosis can be produced in rabbits by the administration of diets containing considerable quantities of cholesterol. I have chosen to call this experimental disease of the arteries "experimental cholesterol arteriosclerosis." The literature bearing on experimental cholesterol arteriosclerosis is reviewed in detail. The results of attempts to produce arterial lesions by cholesterol feeding in animals other than rabbits are described. The data which have arisen from all of these experiments are summarized briefly in Section VII of this paper.

On the basis of these data, the etiology and pathogenesis of experimental cholesterol arteriosclerosis in the rabbit are discussed. It is concluded that the presence of considerable quantities of cholesterol in the diet with a resulting elevation of the level of cholesterol and other lipoids in the blood is essential to the development of the typical arterial lesions in rabbits. It is shown, however, that hypercholesteremia alone cannot be regarded as the cause of the lesions in the arteries. There are preliminary local alterations in the walls of the arteries which precede the precipitation of lipoids. Evidence is advanced to show that these preliminary changes are due to some form of injury to the arteries attendant on the experimental procedure of cholesterol feeding. It is concluded that the occurrence of local changes in the arterial walls, due in all probability to injury of some kind, is the primary event in the development of the lesions of experimental cholesterol arteriosclerosis, an event which is followed subsequently by the precipitation of lipoids in the injured areas.

As a preliminary to the discussion of the significance of the experimental results, a comparison is drawn between the anatomic lesions of experimental cholesterol arteriosclerosis and those of human arteriosclerosis. It is demonstrated that the two diseases are not identical and that there are a number of important differences between them. These differences are of such a nature as to suggest strongly that the rôle of the lipoids in the development of arteriosclerosis as compared with arteriosclerosis in man. A number of normal differences between the rabbit and man which render interpretation difficult and uncertain are pointed out. It is shown that the experimental data are not capable of accurate interpretation without recourse to data on corresponding points derived from the study of human material. With this fact in mind, an attempt is made to correlate the data concerning experimental cholesterol arteriosclerosis with the available information regarding human arteriosclerosis. The three main factors which can be recognized in the etiology of experimental cholesterol arteriosclerosis, namely, cholesterol in the diet, hypercholesteremia, and injury to the arteries, are considered in order as regards their possible signif-

icance in the etiology of human arteriosclerosis. With full cognizance of the inferences which have been drawn in the past from the experimental results, the following conclusions are reached for reasons which are given in their appropriate places:

The results of cholesterol feeding experiments in rabbits do not constitute a valid reason for believing that an excess of cholesterol in the diet plays any rôle in the etiology of arteriosclerosis in man. No convincing evidence in support of such a belief exists at present.

Hypercholesteremia is not found with any regularity in association with human arteriosclerosis. It seems highly probable that arteriosclerosis in man can and usually does develop without deviation of the cholesterol content of the blood beyond the normal limits of variation. In any event, there is no valid evidence to support any other conclusion.

Hypercholesteremia of itself cannot be regarded as a cause of human arteriosclerosis. Although hypercholesteremia, when it occurs, might be expected on theoretical grounds to accelerate the development of arteriosclerotic changes which have already been initiated, there is little evidence at present to indicate the existence of such an effect.

The cholesterol feeding experiments provide no valid reason for believing that a disturbance of cholesterol or lipoid metabolism plays any part in the etiology of human arteriosclerosis. There is no definite or concrete evidence from observations on human beings to support the idea. If a disturbance of lipoid metabolism participates in the etiology of arteriosclerosis in man, the fact remains to be demonstrated in the future.

The initial stage in the development of human arteriosclerosis consists of local changes in the walls of the arteries themselves, changes which are responsible for the subsequent precipitation of lipoids in the affected areas. In man, as in the rabbit, there is every reason to believe that these changes follow as the result of some sort of injury to the arterial walls. As to the cause of this injury, the experimental data yield hardly any information which is capable of application in the human being. Some possible causes of the arterial injury which have been suggested previously and on which the experimental results have some bearing are discussed briefly. Brief comment is also made on the influence of age. No definite conclusions are reached, since it is clear that the cause of the injury to the arteries which is responsible for the development of human arteriosclerosis is unknown.

Following the initial local injury, lipoids are deposited in the injured intima, especially in the intercellular substances. These deposits stir into activity numerous macrophages whch are attracted to the site and which then engulf a large part of the lipoid material. It seems entirely probable that the free lipoid deposits can stimulate the proliferation of connective tissue cells in the intima. This effect is added to that of the original injury to produce a reparative fibrous tissue reaction in the affected areas. If the original injury which initiated the whole process ceases to operate, it is probable that the lipoid deposits prevent immediate healing and continue to exert their influence so that the lesions persist, progressing slowly. Under these conditions, however, it seems likely from the experimental evidence that the lipoids may be slowly removed and may even disappear finally, leaving only a fibrous thickening of the intima. It is unnecessary to assume that a disturbance of cholesterol or lipoid metabolism plays a part in any stage of the process.

This outline of the development of human arteriosclerosis is entirely consistent with the knowledge derived from the study of arteriosclerosis in man, and at the same time it incorporates those inferences which can be drawn with justification from the experimental data. It seems to be the most reasonable working hypothesis which can be constructed from the evidence available.

5. Marked T-wave changes occur before and after thyroidectomy in hyperthyroidism, but they follow no apparent pattern, and their occurrence is unpredictable. The T-waves in hyperthyroidism are not characteristically larger than normal, nor do they necessarily become reduced in size when the hyperthyroidism is relieved.

6. T-wave inversion in thyrotoxicosis does not necessarily indicate the presence of chronic myocardial disease. It occurs quite frequently as a transient phenomenon.

7. The electrocardiographic changes seen in patients with toxic and nontoxic goiter do not seem to be related to (a) changes in heart size, (b) heart rate, (c) postoperative improvement in thyrotoxicosis, (d) duration or severity of thyrotoxicosis, (e) age, (f) sex, (g) the state of cardiac compensation, (h) the presence of substernal goiter, (i) operative injuries to the recurrent laryngeal nerve, (j) the type of anesthesia employed, or (k) the severity of the postoperative reaction.

Altschule, Mark D., and Vook, Marie C.: The Minute Volume Output and the Work of the Heart in Hypothyroidism, J. Clin. Investigation 14: 385, 1935.

1. The minute volume output and the work of the heart are greatly diminished in hypothyroidism following total ablation of the normal thyroid gland.

2. The cardiac output decreases progressively more rapidly than the oxygen consumption as the basal metabolic rate falls in hypothyroidism. This disproportionate decrease in cardiac output is accompanied by a progressive increase in the arteriovenous difference.

3. In most instances the velocity of blood flow was decreased when the cardiac output was low. In some instances, however, the velocity of blood flow did not reflect accurately the work of the heart.

4. The venous pressure, arterial pressure, and vital capacity were not significantly altered after total thyroidectomy in the patients of this series.

Arnett, John H.: Vital Capacity of the Lungs: Changes Occurring in Health and in Disease, J. Clin. Investigation 14: 543, 1935.

1. The vital capacity in two consecutive years was determined in a group of 482 youthful healthy subjects. Deviations from the readings of the previous year proved to be decidedly smaller than those from the hypothetical vital capacity as calculated from the surface area formula of West. The reading of the previous year, therefore, constituted the more reliable basis for vital capacity prediction.

2. In a group of seventy-four cases of acute bronchitis an average diminution from the previously determined healthy figure was noted in both ambulatory and bed cases, a more marked diminution occurring in the latter.

3. The vital capacity is shown before, during, and after illness, in cases of pneumonia, spontaneous pneumothorax, and cardiac decompensation. These observations are believed to be unique.

Boas, E. P.: Angina Pectoris and Heart-Block as Symptoms of Calcareous Aortic Stenosis, Am. J. M. Sc. 190: 376, 1935.

The syndrome of angina pectoris is common in patients with aortic stenosis. It appears to be caused, not by disease of the coronary arteries, but by the narrowing of the aortic valvular opening itself, which impairs the blood supply to both coronary arteries simultaneously. Sudden heart failure in these patients is often followed by symptoms simulating coronary thrombosis.

Auriculoventricular conduction disturbances are also often associated with the calcific form of aortic stenosis. These are determined by extension of the calcific

process into the annulus fibrosus, or ventricular septum. At times a secondary infection of the diseased valve causes heart-block by direct extension into the auriculoventricular bundle. Isolated aortic stenosis is probably of rheumatic origin.

Shambaugh, Philip: Circulatory Changes in Angina Pectoris, Arch. Int. Med. 56: 59, 1935.

Experimental evidence is presented to show that in the dog cardiac pain produced by mechanical constriction of the coronary vessels does not cause a significant rise in blood pressure. On the other hand, the pain response can be precipitated by suddenly raising the blood pressure in the presence of a subminimal constriction of the coronary vessels.

Wolferth, Charles C., Wood, F. C., and (collab.) Bellet, S.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, Arch. Int. Med. 56: 77, 1935.

A group of ten cases is reported in which the electrocardiographic evidence pointed to recent infarction of both the anterior and the posterior wall of the left ventricle. Permission for necropsy was obtained in two of the cases. In each instance an infarct was found involving the lower part of the anterior wall, the apex, and the lower part of the posterior wall.

The electrocardiographic findings were as characteristic as those of recent infarction limited to the anterior or the posterior wall.

The recognition of the signs of acute involvement of both the anterior and the posterior wall removes a source of confusion in the electrocardiographic localization of myocardial infarction.

Chavez, I., and Carvallo, J. M. R.: A New Method for Differentiation of Aortic and Pulmonary Murmurs, Arch. latino am. de cardiol. y hemat. 5: 115, 1935.

The authors describe a method which allows the differentiation of aortic murmurs from pulmonary murmurs, which is useful, chiefly in cases in which the blood pressure, x-ray pictures, etc., are not enough to reach this differentiation.

The method consists in studying the changes undergone by the murmurs under the influence of forced inspiration and expiration and of postinspiratory and postexpiratory apnea.

1. Forced inspiration and postinspiratory apnea produce muffling of the heart sounds and murmurs, especially in the base, with the exception pointed out in the fourth conclusion.

2. Forced expiration and postexpiratory apnea, on the contrary, frankly reinforce all the acoustic phenomena of the heart chiefly in the base.

3. For better appreciation of these phenomena in the base of the heart, the authors recommend the left lateral decubitus combined with the postexpiratory apnea, which are for the phenomena of the base what the Pachon's decubitus is for those of the apex.

4. Systolic murmurs of the pulmonary artery, against the general rule, are frankly reinforced by forced inspiration and postinspiratory apnea while systolic murmurs of the aorta are muffled by the same, a fact which allows their differentiation.

5. Diastolic murmurs of the pulmonary artery are reinforced with forced expiration and postexpiratory apnea in a greater degree than the diastolic murmurs of the aorta which are moderately reinforced.

6. The reason for the reinforcement of the pulmonary systolic murmurs seems to be increase of blood flow through the pulmonary artery during forced inspiration.

Cossio, Dres P., and Berconsky, I.: Coexistence of Syphilitic Aortic Insufficiency and Rheumatic Mitral Disease, Rev. argent. de cardiol. 2: 37, 1935.

The case is reported of a man forty-three years old who contracted rheumatic fever when twenty-eight and syphilis when thirty-five years old. On the basis of the clinical, radiological, and electrocardiographic study, a diagnosis of aortic insufficiency and mitral disease was instituted. The etiological diagnosis offered some difficulties on account of the two heart-affecting diseases that the patient suffered. A syphilitic aortic process and rheumatic mitral process were finally accepted. The autopsy confirmed both anatomical and etiological diagnoses made when the patient was alive. The association of a rheumatic mitral disease with a syphilitic aortic insufficiency is an exceptional one.

Cossio, Dres P., and Menendez, E. B.: Phonocardiographic Studies of Total Auriculoventricular Block, Rev. argent. de cardiol. 2: 1, 1935.

1. Phonocardiograms recorded in cases of total A-V block, including cases of auricular flutter, show the occurrence of a sound whenever there is an auricular contraction; this auricular sound has usually two components distinctly separated one from the other by a short interval.

2. The auricular sound, as shown phonocardiographically, occurs not only during ventricular diastole, but also during ventricular systole, the vibrations being larger in the latter case.

3. The beginning and the first group of vibrations belonging to the auricular sound correspond to the auricular systole and are probably due to the increased tension of the auricular wall and to the compression exerted on the blood contained in the auricular cavity. The fact that the second group of vibrations corresponding to the auricular sound occurs after the auricular systole, suggests an extra-auricular origin; it may be ascribed to ventricular distention, to a change of position, to valvular distention, or to a resonance phenomenon.

4. When the auricular sound proper occurs synchronically with either the first or the second sound, the sound concerned is considerably reinforced. If it occurs during the short silence in the vicinity of either one of the ventricular sounds, it may resemble a reduplication of any of them. If it occurs early during diastole (isometric relaxation or ventricular inflow phases), a sound appears corresponding to the final moments of the ventricular inflow phase, similar in its mechanism of production to a summation gallop sound.

Blackman, S. S., Jr.: Syphilis of the Mitral Valve and Membranous Interventricular Septum of the Heart, Bull. John Hopkins Hosp. 58: 111, 1935.

Two examples of syphilis of the mitral valve and membranous interventricular septum are described, occurring together with aortic insufficiency and typical syphilitic lesions of the aortic valve and aorta.

The lesions in the membranous septum and mitral valve are directly continuous with the syphilitic changes in the root of the aorta and aortic valves. The body of the anterior segment of the mitral valve is therefore chiefly affected, and the posterior mitral leaflet is relatively unaltered.

The gross lesions consist of diffuse leathery thickening of the membranous septum and great anterior mitral leaf. The left ventricular surface of the affected mitral segment and septum may show wrinkling and puckering resembling typical gross syphilitic lesions of the aorta. The mitral chordae tendineae are slightly affected.

Microscopically, gummatous necroses or dense vascular scars with perivascular round cell inflammation, or both, are found in the middle layers of the membranous

septum and the mitral valve. These lesions, continuous with the syphilitic lesions in the media of the aorta, are overlaid by strata of scar tissue formed especially on the left ventricular surface of the valve and septum. Scars and perivascular inflammation are found in the wall of the left auricle and in the muscular interventricular septum near the insertion of the syphilitic mitral valve and membranous septum.

Mitral lesions were suspected clinically in both of the cases described. Each case was characterized by the presence of persistent cardiac decompensation which could not be relieved, lasting for five and a half months in one case of extreme aortic insufficiency, and for a year and a half in the other, in which the aortic valve was moderately insufficient. The anatomical changes in the mitral valve in each case suggested some degree of insufficiency, and it is probable that the mitral lesions were in part responsible for the degree and persistent character of the cardiac decompensation.

Clements, A. B.: Isolated Tricuspid Stenosis of Probable Rheumatic Origin, Am. J. M. Sc. **190:** 389, 1935.

The case of tricuspid stenosis reported presents the following noteworthy features:

1. The extreme degree of narrowing of the tricuspid ostium, resulting in a valve grossly resembling a malformation rather than the end-result of an inflammatory process.
2. The absence of involvement of the other valves, except for a mitral insufficiency and slight sclerosis.
3. The absence of an etiological factor in the history, except for so-called minor rheumatic manifestations.
4. The finding of Aschoff bodies in the myocardium indicating the presence of rheumatic heart disease.
5. The indistinguishability clinically from mitral stenosis.
6. The absence of a pulsating liver and distention of the cervical veins.
7. The slight enlargement of the right auricle in face of the extreme stenosis.
8. The finding of advanced lesser circulation sclerosis, apparently an independent lesion.

Levin, E.: Forms of Hypervolemia in Cardiac Decompensation, Rev. argent. de cardiol. **2:** 17, 1935.

The condition of hypervolemia found in cardiac decompensation does not affect proportionally the blood corpuscles and the blood plasma. Either one of these elements may be predominantly affected, and there can also be mixed forms. The existing form is not simply a transient stage, but a well constituted form, inherent to the nature of the lesion which led to the cardiac insufficiency. Each hypervolemic variety shows a characteristic picture; intense dyspnea, mild cyanosis, and moderate mechanic edema, in cases of hyperplasmia, and the opposite picture in cases of corpuscular hypervolemia.

Book Reviews

ABNORMAL ARTERIAL TENSION. By Edward J. Stieglitz, M.D., New York, 1935, National Medical Book Co., 261 pages with 66 figures.

This volume is similar to one published by Stieglitz five years ago, with the addition of more recent data. It is a coherent account of arterial hypertension and reflects the strong personal views of the author. The book contains much information that is of value in the management and understanding of patients suffering from hypertension or hypotension and will well repay the practitioner who is willing to take the time to read it critically.

Many opinions are expressed as fact perhaps without sufficient regard to evidence to the contrary. For example, bismuth subnitrate is recommended categorically, and literature references are given only to papers of the author, who originated the treatment. Charts are presented which indicate a marked fall in arterial pressure on its administration, but no control period before treatment is shown. Other observers have not been convinced of the value of this treatment, and their views might well have been mentioned.

No attempt has been made to include the original, or indeed in many cases the most important, literature references. Whether this is justified or not, it leads to curious allocation of credit. Quite unconsciously it has also led the author to undue citation of his own publications. For example, much had appeared in the literature on the amyl nitrite test before Stieglitz's publication in 1930.

The theories offered as to the genesis of hypertension are interesting and thought-provoking but cannot be generally accepted as satisfying. It is possible that irritation leads to spasticity, to hypertrophy, to more spasticity, to muscular fatigue, to muscular hyperirritability, to more spasticity and so on, but the proof of it is neither given nor discussed. Stieglitz presents theories in such an enthusiastic and convincing manner that the unwary are likely to accept them as fact. In another edition of his book he might perform an invaluable service by indicating, in marginal notes, problems which are worthy of careful clinical study to prove or disprove his contentions.

In many places in the book he is admirably exact in his statements, but in others he lapses into obscurities which might easily be clarified. The value of the book to the practitioner might be enhanced by more detailed discussion of a number of statements of fact. Thus he states, "A severe proteinuria raises the specific gravity of urine, and it is important that the specimens be at or about 21°C. when examined." It might have been helpful to state how correction is made for the proteinuria to ascertain the nonprotein specific gravity. Again he states in reference to urea and creatinine clearance tests, "The interpretation of the results is not always clear," which may mean almost anything. Dosage of drugs are not given in many cases.

Stieglitz has a low opinion of surgical procedures designed to alleviate and to clarify the mechanism of hypertension. He dismisses them in two and one-half pages. Time alone will tell whether he is correct as regards therapeutic value, but their contribution to knowlege of the mechanism of hypertension should not be underrated.

While there are many suggestions and criticisms a reviewer might make, work by Stieglitz is always welcome as stimulating, interesting, highly individualistic, and thoroughly worth the time required for reading. He does not hesitate to say what he thinks, and a wholesome atmosphere will be created when others express their opinions equally whole heartedly.

I. H. P.

VIER VORLESUNGEN ÜBER KREISLAUFFRANGEN. By Doctor Bruno Kisch, Professor of Physiology at the University of Cologne. Paul Kuschbert, Köln, 1934.

This little volume of sixty-four pages contains four lectures by the author upon timely subjects relating to the physiology and pathology of the circulation, and based chiefly upon his own experimental work. The subjects of the lectures are: "Circulation and Metabolism," "Humoral Blood Changes in Circulatory Failure," "The Circulation and the Autonomic Nervous System," and "The Irradiation of Autonomic Reflexes."

L. A. C.

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Original Communications

THE DEVELOPMENT OF MITRAL STENOSIS IN YOUNG PEOPLE

WITH A DISCUSSION OF THE FREQUENT MISINTERPRETATION OF A MIDDIASTOLIC MURMUR AT THE CARDIAC APEX*†

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A GROSS discrepancy between the clinical diagnosis of rheumatic mitral stenosis and the actual alterations found post mortem has occurred in our experience with sufficient frequency to cause us to study this particular problem. The error in diagnosis has been committed most often in young individuals dying relatively early after the onset of severe rheumatic fever. It became evident as this study progressed that an important source of error was the general unqualified acceptance (in the absence of free aortic regurgitation) of a mid or late rumbling diastolic murmur at the cardiac apex as indicative of mitral valve obstruction (stenosis). Since this murmur may appear during the first few weeks after the onset of rheumatic fever, evidence to be of value in arriving at a correct interpretation of its clinical significance must be obtained largely from post-mortem observation on patients dying at various early intervals after the onset of the disease. Furthermore, it seemed to us probable that this method of approach would contribute considerable information regarding the often repeated question as to the length of time required for the development of important deformity and stenosis of the mitral valve. Previously published reports are of little value in this con-

*From the Massachusetts General Hospital and the House of the Good Samaritan, Boston, Mass. Studies at the latter institution are financed by the Commonwealth Fund, Inc.

†Presented at the meeting of the American Heart Association in Atlantic City, New Jersey, June 11, 1935.

nection since the majority of clinical and pathological studies are concerned largely with older patients and, hence, with long-standing rheumatic valvular disease.

In the present communication we are presenting clinical and post-mortem observations on a group of 100 young individuals with rheumatic heart disease. The series is of sufficient size to warrant certain conclusions as to the evolution of rheumatic valvular disease in general. Special attention has been directed to the development of mitral valve deformity and stenosis. An evaluation of the low pitched rumbling diastolic murmur frequently heard at the cardiac apex and often misinterpreted in such patients is included, together with a discussion of the factors probably responsible for its production.

POST-MORTEM DATA

Our material has been assembled from two sources and consists of the necropsy findings and clinical records of 100 patients twenty-one years of age or younger who showed at post-mortem examination changes in the heart generally attributed to rheumatic fever. Seventy-two of this series constitute the total number which occurred among 7,600 autopsies performed at the Massachusetts General Hospital during the years 1898 to 1935. The remaining twenty-eight represent a similar age group from the necropsy material at the House of the Good Samaritan in Boston, where over 1,200 patients with active rheumatic fever or chorea have received prolonged institutional care and intensive clinical study during the past fifteen years. We have purposely confined the investigation to this special and hence numerically limited group of young people for reasons already discussed. This group also represents the age at which rheumatic fever most frequently occurs and here one may expect a greater degree of accuracy in determining the onset and subsequent course of the disease than is possible in older patients in whom the details of the original infection have been either entirely forgotten or obscured by the passage of years.

A recrudescence of rheumatic infection was the outstanding cause of death in this series and was directly responsible for the fatal issue in eighty-five instances. Postoperative complications accounted for five more deaths, in three of which there was post-mortem evidence of active rheumatic disease also. Subacute bacterial endocarditis caused four deaths, and an acute bacterial endocarditis together with septic disease elsewhere in the body was responsible for three others. Tuberculous meningitis, typhoid fever, and multiple pulmonary abscesses, respectively, killed the remaining three patients. The average age at death for the entire group was thirteen years.

RELATION OF THE DURATION OF THE DISEASE TO THE DEGREE OF MITRAL VALVE DEFORMITY

The interval from the onset of rheumatie fever to death, and the resulting alterations found post mortem in the mitral leaflets have been summarized in Table I. It is to be emphasized that the probable duration as obtained from the elinieal reeords représents a minimal figure, and, where inaccuraeies oeeur, the error is sueh that the duration of the disease is actually longer than indieated.

TABLE I

STRUCTURAL ALTERATION OF THE MITRAL VALVE AND DURATION SINCE ONSET OF RHEUMATIC FEVER—100 CASES

GROUP	1-6 MO.	6-12 MO.	1-2 YR.	2-5 YR.	5+ YR.	?	TOTAL
I. Deformity with anatomical stenosis	0	1*	2	8	12	0	23
II. Deformity without anatomical stenosis	0	0	7	8	10	0	25
III. Slight thickening, no deformity	4	6	7	6	4	3	30
IV. Fresh vegetations, no thickening or deformity	16	4	0	0	0	0	20
V. No vegetations, no thickening or deformity	0	1	0	0	1†	0	2
Total cases	20	12	16	22	27	3	100

*See text for details about this case.
†Moderate aortic valve deformity.

For the purpose of this study the entire series has been arranged in five groups according to the extent of gross alteration found in the leaflets of the mitral valve. Those instances in whieh the scarring was extensive enough to produee any aetual narrowing of the mitral orifiee have been plaeed in Group I. In Group II we have listed the eases whieh showed extensive searring and gross deformity of the valve eurtains, but no anatomieal stenosis of the orifiee. It is of interest that the eireumference of the valve ring as measured along the free edge in the majority of this group was aetually greater than an arbitrary normal figure of 8.5 em. However, the degree of mechanieal handieap imposed upon the heart appears to have been essentially of the same order in this group as in those patients who had aetual stenosis of the orifice. A review of the elinieal eourse and a comparison of the heart weights at neeropsy for the two groups support this impression (Table II). Group III on the other hand is eomposed of those patients who showed on gross examination very slight thiekening of the mitral leaflets usually along the free edge without fusion of the eusps but often with minute fresh vegetations. It is probable that in the majority of this group the funetional handi-

cap to the heart, directly the result of the valvular deformity, was extremely slight. This is supported by the considerably lighter weight of these hearts as compared with that of Groups I and II. Here and in the subsequent two groups we have reason to believe that the valvular involvement per se played no important rôle in the course of the disease.

TABLE II

COMPARISON OF HEART WEIGHT WITH DURATION AND DEGREE OF MITRAL VALVE DEFORMITY

GROUP	NUMBER CASES	AVERAGE AGE AT DEATH	DURATION SINCE ONSET	HEART WEIGHT (93 CASES)
I. Deformity with anatomical stenosis	23	16 yr.	6.3 yr.	480 (2.0)†
II. Deformity without anatomical stenosis	25	14 yr.	5.0 yr.	470 (2.4)
III. Slight thickening, no deformity	30	14 yr.	2.8 yr.	350 (1.8)
IV. Fresh vegetations, no thickening	20	11 yr.	5.0 mo.	269 (2.0)
V. No vegetations, no thickening	1*	4 yr.	8.0 mo.	200 (2.7)
Total group	99*	13 yr.	3.6 yr.	395 (2.5)

*The case with aortic regurgitation and no mitral valve lesion omitted.
†The figures in parentheses represent weight times normal corrected for age.

In Group IV the only macroscopic evidence of valvular alteration was the presence of an active rheumatic endocarditis manifested by a row of minute pinkish gray vegetations along the line of closure. In this group there was no valvular deformity.

Group V consists of only two patients in whom at necropsy there was no demonstrable change of any sort in the mitral curtains. Each is of unusual interest and worthy of special comment. In the first instance listed in column 2 of Table I, the clinical course was typical of severe rheumatic infection in a boy four years of age. There had been acute arthritis at the onset followed by ill health, cyclic bouts of fever, multiple rheumatic nodules, and finally a severe exacerbation with pericarditis, general venous congestion and death at the end of eight months. Apical systolic and diastolic murmurs usually considered pathognomonic of mitral valve deformity (stenosis and regurgitation) were present throughout the illness. At post-mortem examination the heart showed the usual gross dilatation, but the interesting and surprising finding was an entirely normal appearance of the valve leaflets of all four orifices. Careful scrutiny with a hand lens revealed no gross evidence of disease and no vegetations. Histological sections of the myocardium, however, showed changes typical of severe rheumatic carditis. It is of further interest in this connection that Garber[1] has recently collected from the literature seventeen similar cases of extensive rheumatic myocarditis without gross

evidence of valvulitis, to which he has added another case of his own. We will have occasion to comment upon this patient again in connection with a discussion of the significance of apical diastolic murmurs in the absence of important mitral valve deformity. The second case in this group and listed in column 5 of Table I is of interest in that there were present moderate scarring and deformity of the aortic cusps of rheumatic origin without evident disease of the mitral valve. No mitral diastolic murmur had been heard in this instance.

Of the thirty-two patients who died during the first year after the onset of rheumatic fever the majority (twenty) showed minute verrucose vegetations along the line of closure but no other alteration of the mitral leaflets upon macroscopic examination. In ten instances, and usually toward the end of the first year, there was present in addition to verrucose vegetations slight thickening of the free margins of the mitral curtains associated with some shortening and thickening of the chordae tendineae. Actual deformity, if present, was minimal. The two remaining cases were unusual. One of them has already been commented upon in that no evident valvular involvement was present. The final instance of those who died within the first year is exceptional. Well-marked stenosis of the mitral valve was present. In this instance the clinical record, which appeared to be entirely adequate, indicated no symptoms of ill health prior to the onset of typical rheumatic fever nine months before death. It appears significant, however, that well-marked rheumatic heart disease was present when the patient was examined on the second day after the onset of the symptoms of rheumatic fever. At post-mortem examination the mitral orifice showed advanced stenosis admitting only the tip of one finger. In view of the consistent relationship between the duration of the disease and the resulting valvular deformity for the remainder of this group, it is probable that in this apparently exceptional instance the actual onset of active disease antedated by many months the appearance of clinically recognizable symptoms of rheumatic fever. Of this, however, we have no proof.

It is apparent also from Table I that after the first year and often becoming more extensive during subsequent years the structural alterations of the mitral leaflets assume increasing importance. Although considerable deformity may develop during the second year, scarring of sufficient extent to produce stenosis at the mitral orifice is rarely present before the third year. Thereafter the majority in our series (38 out of a total of 52) had developed valvular deformity either with or without actual stenosis of sufficient extent to contribute a considerable mechanical handicap to the functional capacity of the heart.

INCIDENCE AND EXTENT OF COMBINED VALVULAR LESIONS

Table III indicates the relative frequency of valvular lesions. These pathological findings are in close agreement with the experience of Coombs[2] published in 1924, as well as with the figures of others derived from post-mortem findings in adults. In general it is true that when rheumatic endocarditis is present, the mitral valve is involved. One exceptional instance of aortic without mitral involvement has been noted. When combined with other valvular lesions the mitral involvement is the greatest in extent; later, in adult life, fibrotic changes and calcification may alter this relationship. The association of mitral and aortic valve injury occurred in forty-five instances, or almost half the total series. The mitral, aortic, and tricuspid valves were involved in twenty instances; all four valves were injured five times, while the mitral and tricuspid valves were involved without other valve lesions in five instances.

TABLE III

INCIDENCE OF VALVE INJURY

TOTAL	MITRAL	AORTIC	TRICUSPID	PULMONARY	NONE
100	98	71	31	5	1

Calcium deposits were present in the mitral valve ring in ten instances and were invariably associated with gross deformity, consisting in eight cases of marked stenosis of the orifice. These patients represented an older group, the youngest being fifteen years of age; the average duration from the onset of the disease to the time of death was fifteen years.

From a consideration of the data discussed above and summarized in Table I it is clear (1) that the evolution of the early alterations in the mitral cusps as a result of rheumatic fever follows a consistent course, and (2) that the development of important scarring and deformity of the mitral valve requires a considerable length of time.

CLINICAL OBSERVATIONS ON THE SO-CALLED CHARACTERISTIC SIGNS OF MITRAL STENOSIS

A low pitched rumbling, or less often blowing, murmur in mid-diastole or late diastole (often crescendic in character) heard with maximal intensity in the vicinity of the cardiac apex in the absence of free aortic regurgitation is generally considered indicative of mitral valve obstruction sufficient to warrant a clinical diagnosis of mitral stenosis. Furthermore, the presence of an accompanying diastolic thrill or, if the heart rhythm is normal, of a presystolic thrill ending abruptly with the shock of an accentuated first sound, com-

pletes our clinical concept of the classical signs of the more pronounced cases of this lesion. Austin Flint[3] pointed out in 1862 that occasionally an apical middiastolic or presystolic murmur may be found with free aortic regurgitation in the absence of disease of the mitral valve. In 1923 Wood and White[4] expressed the opinion that "diastolic murmurs may occur in certain large hearts with normal valves and lead to a false diagnosis of mitral stenosis. Left ventricular dilatation of high degree seems to be the main factor in such cases, and may perhaps also explain the Austin Flint murmur which is heard only in certain cases of aortic regurgitation."

It has been enlightening to review the structural alterations found post mortem in those of our cases in which mitral stenosis had been diagnosed clinically. In our total series of 100 cases mitral stenosis (with regurgitation) was considered to be present in sixty-eight instances on the basis of a rumbling mitral diastolic murmur (and of a blowing systolic murmur) best heard at the apex of the heart. In addition to the murmurs, an accompanying diastolic thrill was also present in thirty of this group. No instance of so-called "pure" mitral stenosis was encountered. (See Table IV.)

TABLE IV

COMPARISON OF THE INCIDENCE OF MITRAL DIASTOLIC MURMURS AND THRILLS WITH THE DEGREE OF MITRAL VALVE DEFORMITY

GROUP	NUMBER OF CASES	MITRAL DIASTOLIC MURMUR	MITRAL DIASTOLIC THRILL
I. Deformity with anatomical stenosis	23	21 (91%)	13 (56%)
II. Deformity without anatomical stenosis	25	19 (76%)	8 (33%)
III. Slight thickening, no deformity	30	18 (60%)	4 (13%)
IV. Fresh vegetations, no thickening	20	9 (45%)	5 (25%)
V. No vegetations, no thickening	2	1	0

It is a striking fact that of these sixty-eight cases with mitral diastolic murmurs only twenty-one (less than one-third) actually had anatomical stenosis of the mitral orifice. In nineteen additional cases, however, there were present extensive wrinkling and gross deformity of the cusps but no real stenosis; in fact, frequently the valve circumference was equal to or even greater than normal. The remaining twenty-eight cases had either no deformity or at most minimal thickening of the free margin of the valve curtains. Furthermore, in only two of these twenty-eight instances was there also an incompetence of the aortic valves of sufficient degree to suggest that the mitral diastolic murmur might have been an Austin Flint phenomenon. These figures appear even more significant when one considers that the patients were observed

clinically in two institutions where cardiovascular disease, and especially the rheumatic type, receives intensive and specialized study.

There must exist then other and important factors common to this group which offer a more satisfactory basis for the physical signs of apparent mitral stenosis where such does not actually exist. In each case there was present severe and relatively recent rheumatic infection, and marked cardiac enlargement was evident clinically, together with the common post-mortem findings of an hypertrophied and markedly dilated heart with a flabby ventricular wall and the histological picture of diffuse rheumatic myocarditis. Although the valve rings usually share in the general dilatation, their structure is relatively rigid, and the dilatation of the cardiac cavities is in proportion considerably greater. Whether the true explanation of the signs of apparent mitral stenosis in these cases is that of a relative stenosis of the orifice in relation to the dilated ventricular cavity, or if vibrations set up by the diastolic filling of a capacious cavity with relaxed and relatively atonic walls are responsible for the rumbling murmur and the occasional thrill, or if there is a combination of these factors, we are not prepared to say. Of some interest in this connection is the absence of a comparable diastolic murmur in adults in whom with onset of weakness, dilatation, and failure of the left ventricle following long-standing hypertension, aortic valve disease, or recent coronary thrombosis with myocardial infarction a low dull sound in diastole may occur and give rise to a gallop rhythm. The explanation of this difference is not as yet clear. Furthermore, English physicians in the Indian Medical Service have called attention to the fact that severe ankylostoma (hookworm) infection in native children often results in a severe anemia (1.5 to 2.0 million red cell count) and marked cardiac dilatation accompanied by the signs of congestive heart failure. Typical and pronounced apical systolic and diastolic (presystolic) murmurs often occur in these cases showing marked cardiac dilatation. Upon treatment and cure of the infection the heart returns to normal size and the murmurs completely disappear. Gunewardene[5] in 1933 remarked upon the frequency with which a diagnosis of mitral stenosis has erroneously been made in such instances. In three of his recorded cases the heart returned to normal size, and the murmurs disappeared in response to treatment. In the fourth instance a post-mortem examination revealed a dilated heart with a pale and fatty myocardium but no valvular disease. The author believed a "relative stenosis" was the most likely explanation for the murmurs erroneously interpreted as those of mitral stenosis.

DISCUSSION

It is evident that with severe and recent rheumatic infection in childhood when well-marked cardiac enlargement (dilatation) is

known to have occurred within a few months, the presence of a rumbling sound or short blowing murmur in middiastole or late diastole in the vicinity of the cardiac apex in addition to the usual systolic murmur cannot be considered pathognomonic either of mitral stenosis or of any other extensive valvular deformity, but is dependent fundamentally upon severe myocardial disease. This appears to be true even in the presence of an accompanying diastolic thrill and is further supported by our other data recorded above which indicate that a minimum of two or more years must elapse before important valvular deformity occurs. The presence of minute rheumatic vegetations in most of the early cases suggests, however, that ultimately in the course of several years fibrosis and deformity of the mitral valve might have developed to a sufficient extent to have justified our original (but incorrect) clinical diagnosis at the time of the acute illness.

In addition to these clinically as well as pathologically observed cases, we have encountered thirty-two instances out of a total of 950 patients with rheumatic heart disease who at the time of their acute rheumatic fever showed cardiac enlargement and "mitral diastolic murmurs" which were wrongly attributed to mitral stenosis and regurgitation as previously discussed. Four of this group had a corresponding diastolic thrill in addition to a diastolic rumble. At the present time after an average follow-up period of over eight years since the original infection this group of thirty-two patients have clinically normal hearts without murmurs or enlargement. They doubtless represent clinical counterparts of the occasionally observed pathological instances of rheumatic carditis without valvulitis. Further observations on the regression and disappearance of the physical signs of rheumatic heart disease are now in progress and will be reported at a later date.

It is to be added, however, that an apical middiastolic rumbling murmur, as well as the longer murmur with presystolic accentuation, often does mean real mitral stenosis even in childhood, and in some of our older children mitral stenosis rather than ventricular dilatation was responsible for this murmur. The less the evidence of active infection and of cardiac dilatation, the more significant of mitral stenosis is the mitral diastolic murmur. Especially is this the case in adults.

In closing, it may be suggested that the presence of a mitral middiastolic murmur first appearing from a few days to several months after the onset of an acute rheumatic infection may be taken to mean myocardial rheumatism and left ventricular dilatation and perhaps actually serve as another sign of activity of the rheumatic state.

SUMMARY AND CONCLUSIONS

From a clinical and post-mortem study of 100 young patients it has been shown that:

1. The evolution of rheumatic involvement of the mitral valve follows within limits a consistent course.

2. The ultimate development of extensive valvular deformity either with or without actual stenosis of the mitral orifice probably requires a minimum of two years and in most instances a considerably longer period of time. Exceptional cases have been noted.

3. The significance of a mitral diastolic murmur present during the course of active rheumatic fever has been discussed. Evidence is presented to show that in certain circumstances it is not characteristic of mitral stenosis. Myocardial weakness and ventricular dilatation appear to be responsible in these cases for its production.

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THE INFLUENCE OF THE HEAT REGULATORY MECHANISM ON RAYNAUD'S DISEASE*†

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RAYNAUD, in the description of the disorder‡ that bears his name, ascribed its etiology to "a fault of vasomotor innervation," and felt that it "ought to be considered as a neurosis characterized by enormous exaggeration of the excitomotor energy of the gray parts of the spinal cord which control the vasomotor innervation."[10] This conception was so well founded on clinical observation that its acceptance was universal. It was never questioned until the observations of Lewis[7] and Kerr led them to believe that the condition was due to a local fault which "displays itself in hypersensitivity of these vessels to relatively low temperatures." This hypothesis was so divergent from the generally accepted view that it caused renewed interest and experimental research into the fundamental characteristics of the disease. This resulted in the demonstration that, in some cases at least, the hypersensitivity of the vessels to cold was the primary fault. But those who challenged this view pointed out that in many cases the vascular spasm induced by cold was relieved by blocking the vasoconstrictor nerves. They contended that only in advanced cases of the condition was the local fault to cold effective. It was admitted that exposure of the extremity to cold would induce an attack, but it was felt that the cold was merely a stimulus which excites an overactive response of the vasoconstrictor nerves.

As evidence accumulates, it appears that both of these views are correct. The difference exists in the reaction of individual patients. Some have a vasomotor neurosis that is relieved by blocking the vasoconstrictor nerves. In others, sympathetic denervation has only a slight effect and will neither prevent nor relieve attacks of vascular spasm in the extremity subjected to appropriate degrees of cold. In both, whether it is primary or secondary, there is hypersensitivity to cold.

Emotional factors form another influence that calls forth an exaggerated response. In the normal person, emotion produces peripheral vascular changes. We speak of the "pallor of fear," the "blush of

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†Read before the American Heart Association, Atlantic City, June 11, 1935.

‡The term "Raynaud's disease" is used in its commonly accepted sense to denote a severe idiopathic vasospastic condition of the extremities. It may well be a symptom-complex rather than a disease entity.

embarrassment," or of an apprehensive person having "cold feet." Yet attacks of pallor, cyanosis, and pain do not occur in the extremities of normal persons as they do in patients with Raynaud's disease, in spite of the fact that the emotional stimulus may be the same in both. Nor does cold play a part here for these vasospastic attacks from psychic disturbance occur when the extremities are warm.

Recently Smithwick, Freeman, and White[13] have made the important observation that after sympathetic denervation the part becomes sensitized to epinephrine. They record the striking example of gangrene in such a sensitized extremity resulting from emotional disturbance. This was apparently due to excessive vasoconstriction induced by the patient's circulating adrenin.

There is evidence to support the view that the peripheral vessels in Raynaud's syndrome may be hypersensitive to cold, to vasomotor impulses, to emotion and, after sympathectomy, to epinephrine. This being true, it is possible that any normal stimulus may give an exaggerated vascular response. It leads to the conception that there is a local abnormality which causes an excessive reaction when normal stimulation is applied. If this were the case, then it is reasonable to suppose that body heat regulation would have influence, for this is one of the most important functions of the peripheral vasomotor mechanism. The skin of the extremities makes up about 65 per cent of the body surface. Its vessels are frequently constricting or dilating to perform the thermoregulatory functions of heat conservation or dissipation. With slight alteration of body temperature there is normally a wide fluctuation in that of the extremities.[3,4] Consequently, if the peripheral vessels in Raynaud's disease are hypersensitive to normal stimuli, then alteration in body temperature should induce or relieve attacks of vascular spasm. The following experiments were designed to test this.

METHODS

Four typical patients with Raynaud's syndrome who had previously been studied by Morton and Scott[9] were readmitted. Two had severe cases of long standing. One of these had had loss of tissue from trophic changes. The majority of the studies were conducted with these cases. For the sake of comparison, the other two cases chosen were less severe, their attacks were not as painful nor as prolonged as in the severe cases and could be abolished by nerve block.

Observations were made in a constant temperature room at 19° to 21° C. Skin temperature readings were obtained with the dermatherm.[11]

The First Question.—If the hands are kept warm and the body cooled, will vascular spasm occur?

The hands may be warmed by covering them with blankets, a warm box, warm water, or electric pads, leaving the finger tips exposed for temperature readings. The body may be cooled by exposure to cold air as in an ice box, by a cold bath, or by drinking large amounts of ice water.

Experiment 1.—April 3, 1935. Subject F. B. S.M.H. 38360 (severe case). Room temperature 21.1° C.

The patient came to the constant temperature room from the division. The hands were slightly blue but not deeply cyanotic or painful. Preliminary temperature readings showed the digits to be 21° C. at 11 A.M.; the hands and forearms were placed in water at 42° C., the finger tips being exposed for temperature readings.

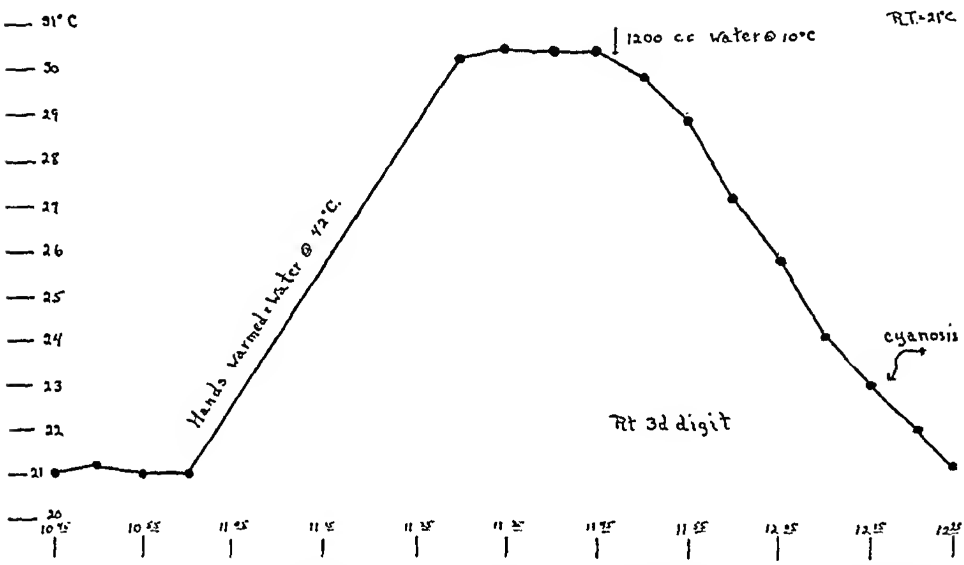

Fig. 1.—If the hands are kept warm, cooling the body causes vascular spasm in these extremities. The hands were warmed in water at 42° C. until they reached the vasodilatation level. The body was then cooled by drinking 1,200 c.c. of ice water. This caused a fall in the temperature of the finger tips and the onset of an attack of vasospasm with pain and cyanosis.

At 11:30 A.M. the temperature of the digits had risen to 30.2° C. The hands were pink; there was slight perspiration of the face; and the patient felt warm. At 11:45 he drank 1,200 c.c. of water at 10° C. This caused an immediate decline in the temperature of the fingers. At 12:05 he complained of feeling chilly. At 12:15 the hands became cyanotic. The temperature of the fingers was 23° C. Within ten minutes the temperature had fallen to 21° C. and there was vascular spasm with cyanosis and pain (Fig. 1).

I find one mention of a similar experiment. Simpson, Brown, and Adson[12] report their experience with two cases. In one, the patient, with hands wrapped in a blanket (temperature of fingers 33.4° C.), was left in an ice chamber at 2° C. for five minutes. In spite of the warmth of the hands, vascular spasm occurred. In another, the hands

were submerged in water at 38° C. and the patient was placed in the ice chamber for thirty minutes. Exactly the same result occurred.

It would appear that even with the hands warm, attacks of vasospasm may be induced by cooling the body.

The Second Question.—Will warming the body relieve vasospasm of the extremities?

This has already been answered in the affirmative by Lewis and Pickering.[8] They state that "it is clear that warming the body in Raynaud's disease will release digital arteries previously held constricted by cold." In their experiments a chamber heated with carbon arc lamps was used to warm the body. Other methods are the use

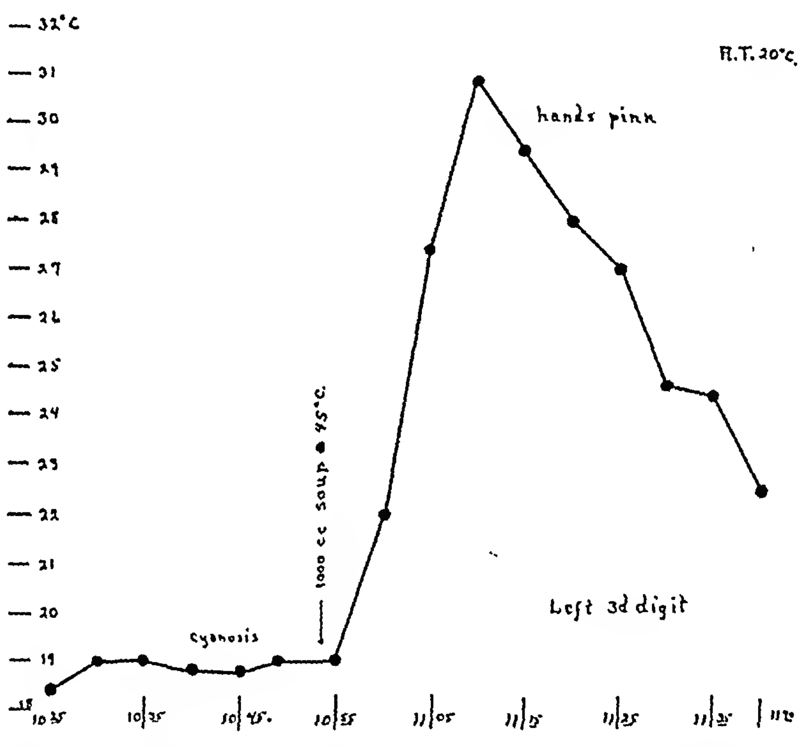

Fig. 2.—Warming the body will relieve an attack of vascular spasm even though the hands remain in a cool environment. In this experiment the subject's hands were very cyanotic and painful. She drank 1,000 c.c. of soup at 45° C. with resultant increase in temperature of the fingers and relief of the vasospasm. Other forms of warming the body, as by external heat, have the same effect.

of hot baths,[4] diathermy, wrapping the body in blankets,[3] or the drinking of hot liquids. That the latter will produce the effect is shown by the following experiment.

Jan. 10, 1935. Subject B. L. S.M.H. 19608. Room temperature 20° C.

The patient came to the examining room from out of doors. The hands were deeply cyanotic and painful. The temperature of the fingers was 18.4° C. She was observed from 10:25 until 10:55 A.M. without noticing any appreciable change in symptoms, appearance, or temperature. At this time she drank 1,000 c.c. of soup at 45° C. There was an immediate rise in the temperature of the fingers. In twenty minutes the temperature of the digits was 31° C. All evidence of vasospasm

disappeared, and the hands turned a normal pink color. The temperature of the digits soon fell, but symptoms did not return (Fig. 2).

The Third Question.—Can warming of the body prevent attacks of vasospasm if the hands are exposed to appropriate degrees of cold?

March 4, 1935. Subject C. D. S.M.H. 4638. Room temperature 21° C.

The patient came to the examining room from the division. The hands were cyanotic but not painful. The temperature of the fingers was 21° C. After preliminary observation for fifteen minutes the body was warmed by blankets and a rubber sheet.[3] Forty minutes later the digits were pink and warm, all spasm having been relieved. Their temperature had risen to 30.8° C. At 3:10 P.M. with the body kept warm the hands were submerged in water at 15° C. leaving the finger tips exposed. At 3:20 P.M. the temperature of the digits had fallen to 20° C..

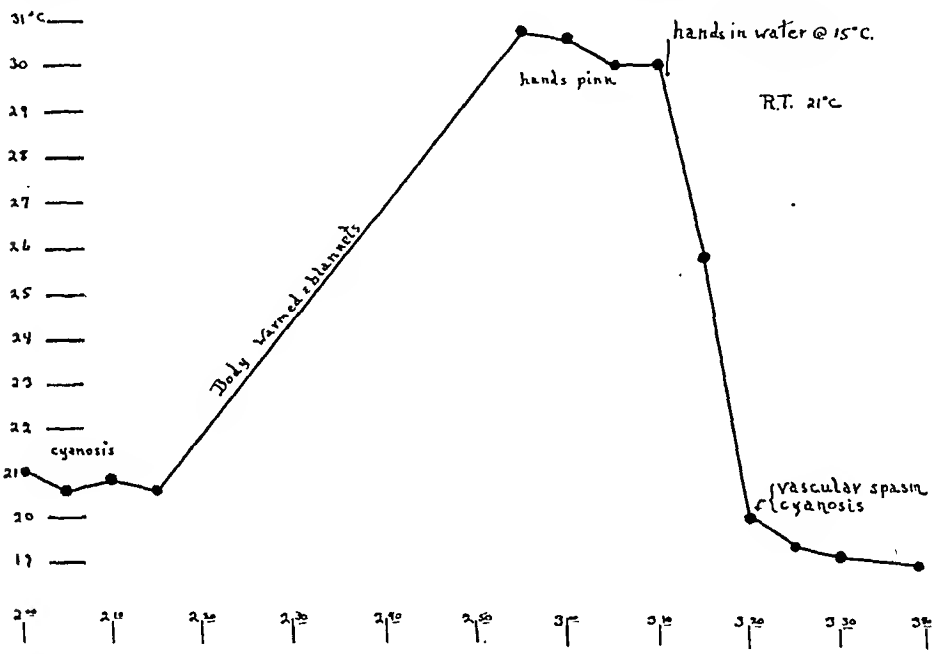

Fig. 3.—Keeping the body warm will not prevent an attack if the hands are subjected to appropriate degrees of cold. Here the subject's body was warmed in blankets until the hands reached the vasodilatation level. In spite of this, vascular spasm with pain and cyanosis occurred when the hands were placed in water at 15° C.

and vascular spasm with cyanosis and pain occurred. The experiment was discontinued at 3:40 because of the discomfort from the vasospasm (Fig. 3).

It is seen that warming the body did not prevent an attack of vascular spasm when the extremities were subjected to cold. This is in line with the conception that local exposure to cold forms the strongest stimulus to vasospasm in this condition.

The Fourth Question.—Is the heat derived from the digestion of food sufficient to prevent or relieve vasospasm?

It has been shown that the ingestion of food results in an increased blood flow.[5] Further, that during digestion there is an increase in both the body and skin temperature.[1] This has been confirmed.[6] The

"specific dynamic action" of the food increases body heat with consequent peripheral vascular dilatation to dissipate the surplus. It was reasoned that this effect might be utilized to prevent or abolish attacks of vasospasm in Raynaud's syndrome. If the "internal fires" were kept burning, there would always be a positive heat balance and hence little stimulus to vasoconstriction. Moreover, this would prevent hypoglycemia which has been shown[2] to stimulate the secretion of adrenin and so bring about vasospasm.[13]

The subjects were fed high protein meals containing 200 gm. of lean meat as well as high carbohydrate meals. Coffee or tea was not used, nor was the heat of the food sufficient to give an effect. There was no consistent alteration in the surface temperature of the digits at the time of eating nor for two hours after such meals. Attacks of vasospasm could be induced by exposure to cold and once instituted were not relieved by food. So it is seen that the test of this question gave negative results. But I am not at all satisfied with the findings. It is desirable that further study be done along this line, observing the subjects in a calorimeter rather than in a constant temperature room. In this way a more accurate check may be made upon their response to food. This is desirable, for, if the "specific dynamic action" of frequent feedings would diminish or prevent the attacks of vasospasm, it would be of some value in treatment.

SUMMARY

The influence of body heat regulation was observed in cases of Raynaud's disease. It was found that: (1) with the hands kept warm, cooling the body will cause an attack of vasospasm; (2) warming the body will relieve an attack; (3) warming the body will not prevent an attack if the hands are exposed to cold; and (4) the warming effect of food was inadequate to influence the vasospasm.

It is concluded that body heat regulation may have influence on the vasospasm of Raynaud's disease. This constitutes further evidence that normal forms of stimulation may give rise to an exaggerated vascular response. It suggests that a local abnormality causes this excessive spastic reaction from several diverse motivating factors.

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THE EFFECT OF OUABAIN UPON THE ELECTROCARDIOGRAMS OF SPECIFIC MUSCLE LESIONS*

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INTRODUCTION

THE effects upon the electrocardiogram caused by experimental ligation of the blood supply to a single ventricular muscle band in dogs have been described in a series of papers from this laboratory.[1-4] These same alterations have also been found to appear in electrocardiograms of monkeys (*Macacus rhesus*),[5] whose hearts are more similar to that of man.

If displacements of the R-T interval have a clinical application in localizing the site of a coronary obstruction and as a guide to treatment, then to know the effect of the digitalis group upon this interval is important.

In 1915, Cohn[6] observed that in man digitalis causes an inversion of the T-wave and also stated that, if the T-wave is initially negative, upon digitalization it again becomes positive. This action is not influenced by atropine and hence the seat of action is said to be in the muscle. Cushny[7] and Sollman[8] also describe vagal and direct muscular actions of digitalis.

EXPERIMENTAL PROCEDURE

Experiments have been devised to determine whether digitalis had an effect upon the R-T segment displacement which results from lesions in specified muscles.

Observations were made on six monkeys (*Macacus rhesus*) and five dogs. Because only acute experiments were feasible, ouabain was given intravenously. In some cases the animals were first given a therapeutic dose (0.05 mg. per kg.) and when its effects had developed (judged by flattening of T and prolongation of P-R), a muscle lesion was produced. In other experiments the lesion was produced first and the animal then given a toxic dose of ouabain (0.1 mg. per kg.). The operative procedure and other points of technic were the same as described previously.[1, 3] The hearts were removed at autopsy and subsequently dissected to establish the exact locations of the lesions.

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RESULTS

Previous therapeutic dosage of ouabain did not prevent the appearance of the R-T change known to be characteristic of specific muscle lesions. Toxic dosage of digitalis did not affect the lesion electro-

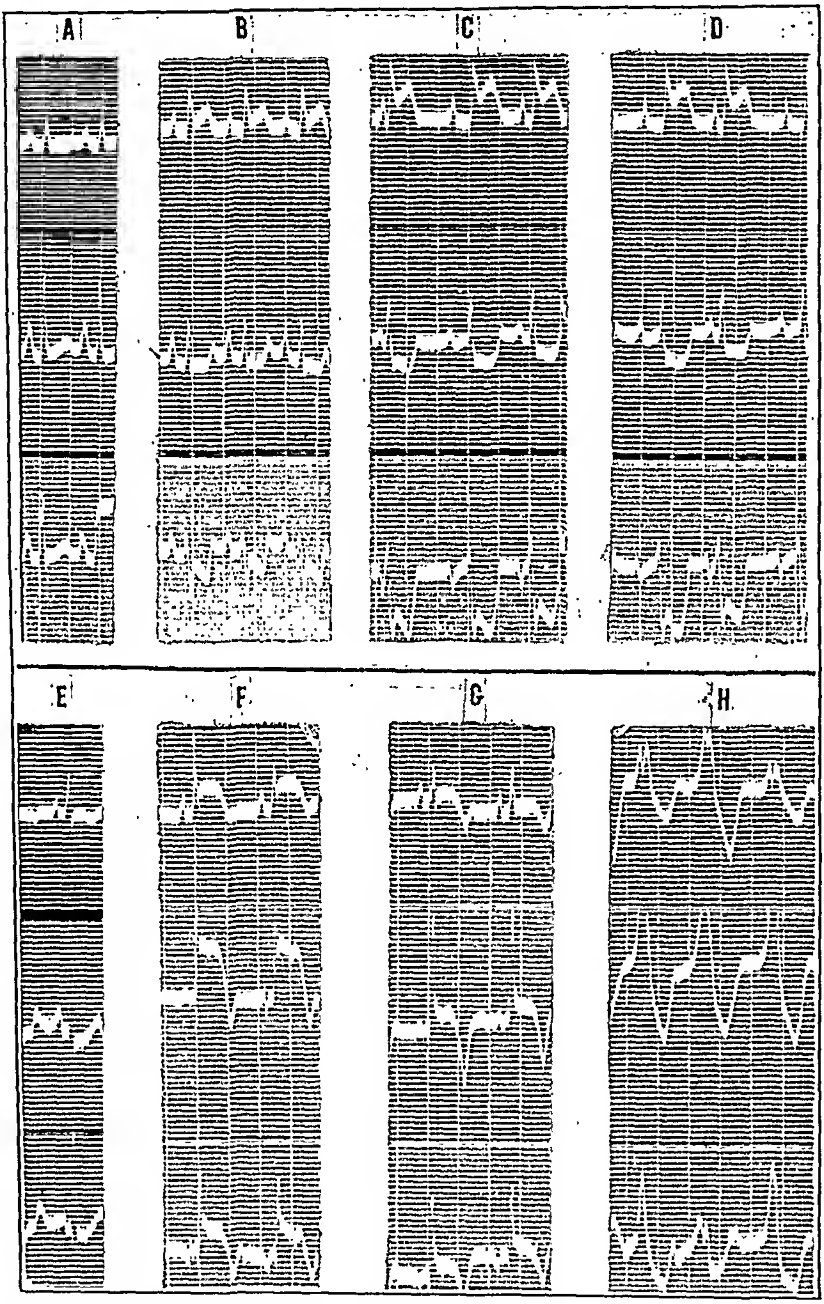

Fig. 1.—All tracings show simultaneous leads (I, II, and III from above downward). *A* is a control record; *B*, following a lesion of the DSS muscle; *C* and *D* show this characteristic alteration to be exaggerated by therapeutic and toxic amounts of ouabain, respectively.

E is a control record; *F*, following a lesion of the DBS; while *G* and *H* show the tendency of therapeutic and toxic doses of ouabain to remove the effect characteristic of the muscle lesion.

cardiograms of different muscles in the same manner, hence one must present data and discuss each muscle separately.

In Table I are summarized the changes in T and R-T under therapeutic and toxic dosage of ouabain for comparison with the changes in the untreated muscle lesion.

TABLE I

MUSCLE	R-BASE INEQUALITY EXPRESSED IN 0.1 MV. MUSCLE LESION			R-BASE INEQUALITY EXPRESSED IN 0.1 MV. MUSCLE LESION PLUS OUABAIN		
	LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
SSS	+1.0	+1.3	+1.0	+0.3	+0.25	±0.0
SBS	-1.0	+2.0	+1.5	-0.3	+1.5	+1.1
DSS	+1.5	-1.5	-2.5	+1.0	-2.75	-5.0
DBS	+3.0	+5.25	+2.5	+0.5	+1.5	+1.1

In the case of the superficial muscles, ouabain in therapeutic amounts has little effect either on the T or R-T. In toxic doses the R-T shifting in all leads is reduced.

When a *deeper* muscle is anemic, the effects of ouabain are far more pronounced. If the drug is given in therapeutic amounts before ligation of the branches from the left circumflex to the deep bulbospiral, the marked elevation of R-T still occurs but this is followed by a very negative T, whereas in the untreated condition the T is wholly positive (Fig. 1 *F*). If the ouabain concentration is increased to toxic amounts, the R-T shoulder drops toward the isoelectric level, and the T becomes progressively more negative until the heart stops.

Lesions in the deep sinospiral muscle in the presence of ouabain produce quite a different electrocardiographic picture (Fig. 1 *A* to *D*). Therapeutic dosage leaves the elevation of R-T in Lead I relatively unaltered but markedly augments the already existing depression in Leads II and III. As toxicity intervenes, the elevation in Lead I and the depression in Leads II and III are still further exaggerated until just before death, when the voltage suddenly decreases.

All of these tracings have been read with a Cambridge measuring instrument. In Table II are presented average results along with control data. (a) As would be expected, the muscle lesions had no effect upon the P-R interval, for the vessels ligated were definitely

TABLE II

	P-Q	QRS	QT	ST	RATE
Dogs—pentobarbital 50 mg./kg.	0.098	0.041	0.229	0.175	168
Monkeys—pentobarbital 50 mg./kg.	0.069	0.027	0.245	0.216	161
Dogs—pentobarbital + muscle lesion	0.091	0.039	0.237	0.189	141
Monkeys—pentobarbital + muscle lesion	0.087	0.032	0.361	0.300	113
Dogs—pentobarbital + muscle lesion + ouabain	0.128	0.042	0.290	0.236	80
Monkeys—pentobarbital + muscle lesion + ouabain	0.170	0.058	0.404	0.322	35

chosen so that the blood supply to the conduction system would be unaffected. The P-R interval is lengthened by ouabain. (b) The QRS also is uninfluenced by the muscle lesions, but, as toxicity under ouabain appears, the interval becomes greater. These data would support the opinion that the muscle lesions do not interfere with the spread of excitation as indicated by the duration of QRS. (c) The Q-T and S-T are increased by the muscle lesions and still more by the ouabain. This fact, together with the observed effects upon the R-T and T phases, seems to indicate that the effect of the lesions is upon portions of the contractile mechanism without involving the chief conducting pathways. This increase in Q-T and S-T cannot be relieved by vagal section, nor are the displacements of R-T altered either during vagal stimulation or after vagal section. Three observations, then, support the supposition that the changes in the electrocardiogram consequent to anemic infarcts are produced by injuries to muscular rather than to nervous structures: (1) These changes occur if the vagi are cut and are uninfluenced during vagal stimulation; (2) these characteristic changes are influenced by ouabain in that part of the electrocardiogram where ouabain has been stated to exert its effect by direct action on the muscle; (3) the S-T and Q-T are prolonged by these infarcts whereas the QRS is not.

It is not considered that there are data either in the literature or in these experiments which would differentiate between an action upon muscle fibers or upon the peripheral ramifications of the Purkinje material within the muscle bands.

SUMMARY AND CONCLUSIONS

1. Anemic infarcts localized to one ventricular muscle band have been produced experimentally in dogs and monkeys.

2. The electrocardiographic change produced is characteristic for each muscle.

3. Ouabain in therapeutic doses does not prevent the appearance of these characteristic changes in the electrocardiogram.

4. Ouabain in toxic doses tends to diminish the electrocardiographic change characteristic for three muscles, namely, the superficial bulbo- and sinospiral, and the deep bulbospiral muscle.

5. Ouabain in therapeutic and toxic doses tends to increase the electrocardiographic change found to be characteristic for the deep sinospiral muscle.

6. Neither the R-T or T changes due to the muscle lesions nor those due to the ouabain are influenced by vagal section.

Grateful acknowledgment is made to the Hendricks Fund of Syracuse University, to the Committee on Scientific Awards of the American Medical Association, and to the Ella Sachs Plotz Foundation, each of which has some part of the expense of this research.

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THE RESULTS OF TREATMENT IN CARDIOVASCULAR SYPHILIS*

A Report of Three Years' Additional Observation

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In 1930 one of us (J. E. M.) with Danglade[1] presented to this association a preliminary report on the treatment of cardiovascular syphilis, based upon a study of 141 patients. The conclusions reached were later amplified and extended in a detailed analysis of 165 cases published with Danglade and Reisinger[2] in 1932. The preliminary report included eight cases in which the diagnoses might be questioned; the later study was purposely limited to patients with saccular aortic aneurysm or syphilitic aortic insufficiency.

When this study was completed on July 1, 1931, an effort had been made to trace each of the patients, numbering a few over 300, with definite diagnoses of saccular aortic aneurysm or syphilitic aortic insufficiency, whose names were in the files of the Syphilis Division, and the 165 reported included all whose status could be determined as of that date.

In evaluating the usefulness of specific therapy in these conditions, the patients were divided into four groups on the basis of the amount of treatment they had received; and it was shown, we thought, that properly directed antisyphilitic treatment resulted in alleviation of symptoms and prolongation of life, with consequent reduction in mortality rate for an incomplete period of observation.

Many remained unconvinced, however, and Barnett,[3] in criticizing the method of study employed and in reporting his own experience, concluded that there was no evidence to indicate that antisyphilitic treatment is beneficial to patients with aortic insufficiency or aneurysm. It seemed wise, therefore, to reexamine the subject.

The present study deals with the same group of patients previously reported.[2] On July 1, 1931, 109 of the 165 discussed were dead. Four of the fifty-six who remained alive could not be traced; the remainder have been followed up to Jan. 1, 1935, thus forming a group of 161 patients in which the mean potential period of observation has been ten years and eight months, with a minimum period of observation of any living patient of five and a half years. No effort was made

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Read before the American Heart Association, Atlantic City, N. J., June 11, 1935.

to add additional cases; it was thought that the long period of observation available in this group was the most valuable feature of the study.

The data which bear on the evaluation of antisyphilitic treatment have been entirely recalculated and several changes in the method of analysis have been made. Duration of life is expressed as mean instead of as average, in order to facilitate the determination of the statistical significance of differences. The information concerning causes of death has been again reviewed, and the deaths divided into those directly due to cardiovascular syphilis, and those due to other diseases, or due to unknown causes.

A simpler division into two treatment groups has been substituted for the four groups of the former report. In an "inadequate treatment" group have been placed those patients who received the equivalent of one course of an arsenical, or a long course of heavy metal, or less; while the "adequate treatment" group includes those who received a course of an arsenical plus heavy metal, two long courses of heavy metal, or more. Such a division is arbitrary and the minimum of the latter group may not truly be said to constitute adequate antisyphilitic therapy. Fortunately in this series, however, there was little gradation about the dividing line; the majority had received either very small or relatively large amounts of treatment.

The most important change in the method of analysis was suggested by Barnett's[3] well-taken exception to the propriety of including in the "inadequate treatment" group those patients who, because of an originally bad prognosis, died so soon that adequate treatment could not have been given. Accordingly, and as a result of studies to be elaborated elsewhere,[4] which show that those dying quickly should be considered as a separate group, the fifty-three patients (33 per cent of the total) who died within less than a year after they came under observation have been removed from a consideration of therapeutic results.

As in the previous paper, duration of life has been calculated from the onset of symptoms referable to the cardiovascular system, or to the establishment of a definite diagnosis in the few instances in which symptoms were indefinite. This obviously introduces some uncertainties, but no more applicable method has been suggested.

An effort had been made to give to every patient adequate antisyphilitic treatment; excluding those who died quickly, patients were inadequately treated only because of lack of cooperation. In this regard Barnett[3] has suggested that patients who are so uncooperative that they fail to return for treatment also do not follow instructions in regard to limitation of activity and general medical care, and that

therefore untoward results in such a group should be charged to lack of therapy in general, rather than to lack of antisyphilitic treatment. The individual variation in ability to understand and willingness to follow instructions is so great as to prohibit generalizations of this sort, and careful study[4] has convinced us that our "inadequate treatment" and "adequate treatment" groups vary in no way from each other, as to the apparent severity of their illness or the kind and extent of general medical care, except only in the amount of antisyphilitic treatment received.

Table I shows that the 161 patients are almost equally divided into three groups. One-third of them died within less than a year of observation, and with few exceptions received no antisyphilitic treatment, mainly because the onset and progress of their fatal illness was so abrupt as to exclude its possibility. Another third survived for more than one year but received inadequate treatment. The remaining one-third fell into the "adequate treatment" group. Fifteen (29 per cent) of the 52 patients with aneurysm and 38 (35 per cent) of the 109 with aortic insufficiency died within the first year of observation; 17 (33 per cent) of those with aneurysm and 36 (33 per cent) of those with aortic insufficiency received inadequate treatment; while 20 (38 per cent) of the patients with aneurysm, and 35 (32 per cent) of those with aortic insufficiency, were adequately treated. The distribution of cases is therefore quite symmetrical.

TABLE I

THE DISTRIBUTION INTO GROUPS OF 161 CASES OF CARDIOVASCULAR SYPHILIS

	NUMBER OF CASES	NUMBER PATIENTS DEAD	ANEURYSM		AORTIC INSUFFICIENCY	
			NUMBER OF CASES	NUMBER DEAD	NUMBER OF CASES	NUMBER DEAD
Total	161	123	52	41	109	82
Died in less than one year	53	53	15	15	38	38
Total, inadequate treatment and adequate treatment	108	70	37	26	71	44
Inadequate treatment	53	46	17	14	36	32
Adequate treatment	55	24	20	12	35	12

Of the 108 patients available for a consideration of the results of treatment, 53 (49 per cent) received inadequate treatment, and 55 (51 per cent) were adequately treated. The "inadequate treatment" group includes 17 individuals with aneurysm and 36 with aortic regurgitation; the "adequate treatment" group comprises 20 with aneurysm and 35 with aortic insufficiency.

This study may be considered complete only when all of the patients are dead, but in the meantime a comparison of the mortality

rates of the two groups affords valuable information. Figure 1 presents such comparison. Fourteen (82 per cent) of the 17 patients with aortic aneurysm who received inadequate treatment are dead; and in eleven of these (65 per cent) death was due to the cardiovascular disease. In contrast, 20 patients with aneurysm were adequately treated; 12 (60 per cent) of these are dead, but only 8 (40 per cent) died from cardiovascular syphilis. In those patients with aortic insufficiency, the reduction in mortality due to cardiovascular syphilis is even more striking. The numbers receiving inadequate and adequate treatment are almost exactly equal. Thirty-six were inadequately treated, and 35 received adequate treatment. Thirty-two (89 per cent) of the former are dead, twenty-three of them (64 per

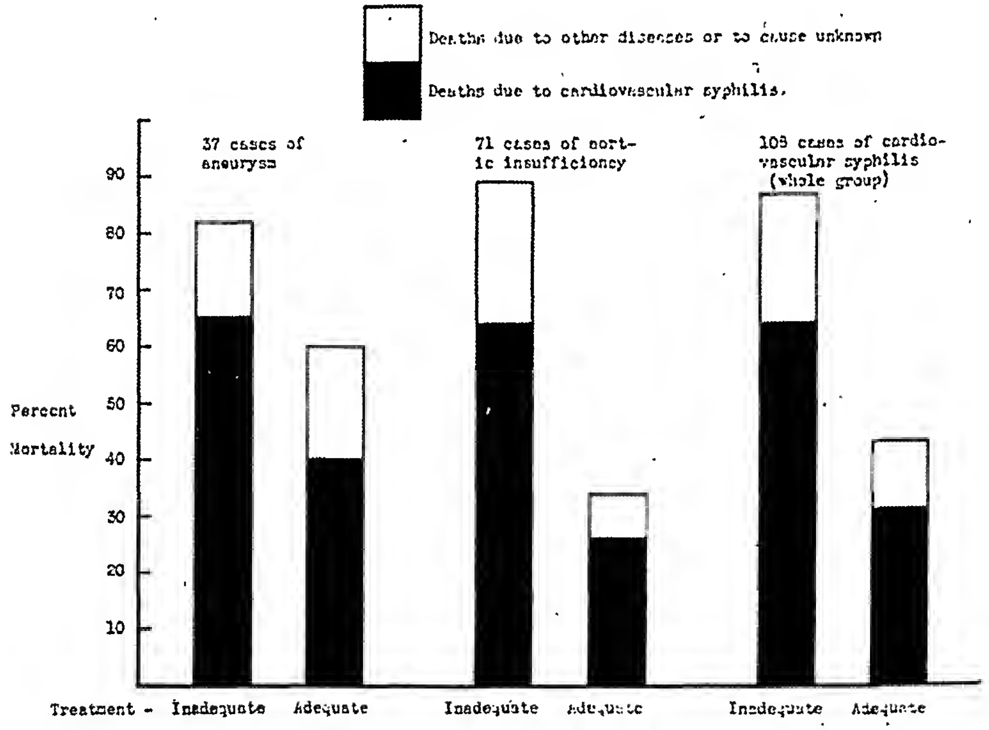

Fig. 1.—The mortality rate of 108 patients with cardiovascular syphilis observed for more than one year in reference to the amount of antisyphilitic treatment received.

cent) from heart disease; while only 12 (34 per cent) of the latter have died, and only 9 (26 per cent) of these from cardiovascular syphilis.

Considering the group as a whole, 46 (87 per cent) of the 53 inadequately treated patients are dead, while only 24 (43 per cent) of the 55 well-treated have succumbed, while deaths known to be due to cardiovascular disease are 34 (64 per cent) in the former, and 17 (31 per cent) in the latter.

Figure 2 contrasts the duration of life from the onset of symptoms to death in the seventy treated patients who have died. Of the patients with aneurysm the fourteen dead who were inadequately treated

lived a mean of thirty-two months after developing symptoms, while the twelve who had received adequate treatment lived fifty-five months. In those with aortic insufficiency the 32 dead who had been inadequately treated lived a mean of forty-five months, and the twelve dead in the "adequate treatment" group lived sixty-one months.

Again considering the group as a whole, the 46 inadequately treated patients survived for a mean of forty-one months after the development of symptoms, while the 24 who received adequate treatment lived for sixty months.

In a later communication[4] we shall demonstrate in detail that the differences between the two treatment groups are statistically signi-

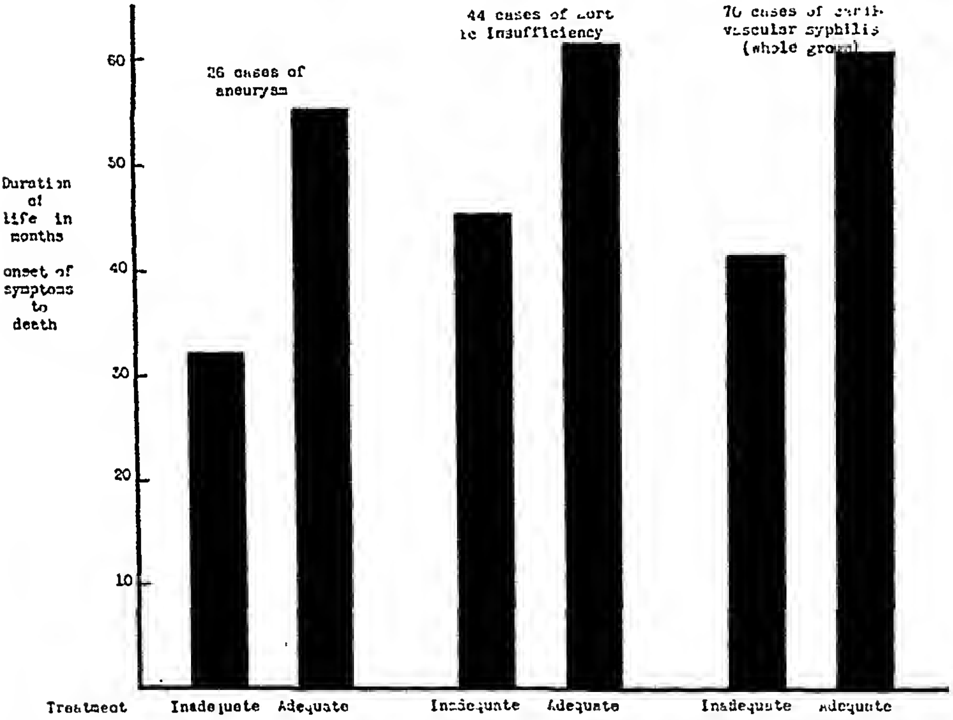

Fig. 2.—The duration of life in seventy dead patients who had cardiovascular syphilis and were observed for more than one year in reference to the amount of treatment.

ficant, with the exception of the difference in duration of life between adequately and inadequately treated patients with aortic insufficiency. There the number dead who were adequately treated was so small and the durations observed in the individual cases were so variable that from the statistical standpoint a large probable error is introduced.

The full significance of these figures may be appreciated only by comparing the observed duration of life in those dead with the mortality rates of the two groups. The surviving patients in both groups have lived on the average approximately ten years, i.e., far in excess of the duration of life in those already dead. However, only 7 of the

53 patients inadequately treated survive, while 31 of the 55 adequately treated are still alive. It is readily apparent that when all of the patients are dead, the duration of life in the well-treated group will be vastly in excess of the survival period of those poorly treated.

Confirmation of our proof as to the value of treatment in cardiovascular syphilis has been provided by Grant.[5] In the course of his monumental study of the clinical course of a thousand patients with heart disease, 189 patients with syphilitic aortic insufficiency were followed either to death or for a minimum observation period of ten years. Part of these had been allowed to go without antisyphilitic therapy, a larger group had been given potassium iodide, and the remainder had received potassium iodide and neoarsphenamine in

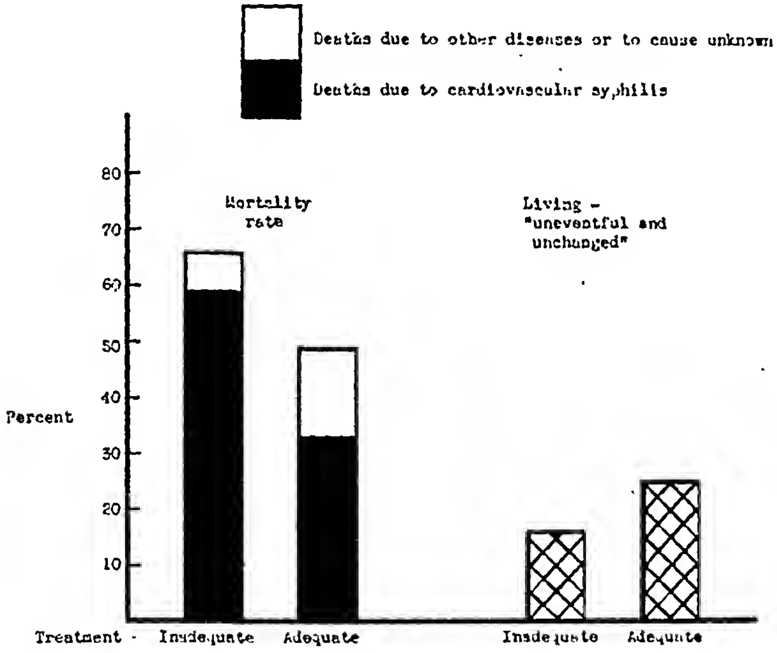

Fig. 3.—The outcome in 171 patients with syphilitic aortic insufficiency (after Grant).

varying amounts, with interval mercury by inunction. The general medical care was the same for all groups.

We have analyzed the very complete data given by Grant for each case by the same methods employed for our own. Eighteen of the cases were deleted because of inadequate information. Of the 171 remaining, 51 had received at least one course of six injections of neoarsphenamine, mercury by inunction, and potassium iodide by mouth; 75 had received potassium iodide by mouth only; and 45 had been given no antisyphilitic treatment. Grant's study and our reanalysis revealed no significant differences between these last two groups, which have therefore been consolidated to form an "inadequate treatment" group, while the former was considered as an "adequate treatment" group.

Figure 3 contrasts the mortality rate and the number living, in Grant's words, "uneventful and unchanged," in the two groups. Twenty-five (49 per cent) of the 51 patients who received specific therapy were dead at the end of ten years; in 17 (33 per cent) death was due directly to cardiovascular syphilis. Of the 120 patients in the "inadequate treatment" group, 79 (66 per cent) died during the same period; 71 (59 per cent) from cardiac disease. In contrast to this, 13 (25 per cent) of the adequately treated, but only 19 (16 per cent) of the inadequately treated, had survived the ten-year period to be adjudged "uneventful and unchanged." There was no significant difference in the duration of life between the well- and poorly treated groups.

SUMMARY

1. An analysis of the course of 161 patients with outspoken forms of cardiovascular syphilis is presented with reference to the effect of antisyphilitic treatment. Fifty-two of the patients had saccular aortic aneurysm; 109 had syphilitic aortic insufficiency.

2. One-third (53) of the patients died in less than a year of observation, and these are considered in a separate group, as unamenable to the beneficial effects of specific therapy because of the gravity of their disease and its rapid progress.

3. One hundred and eight survived for more than a year of observation and received varying amounts of antisyphilitic treatment. Of these, 53 are considered in an "inadequate treatment" group and 55 in an "adequate treatment" group.

4. The mean potential period of observation was ten years and eight months.

5. The mortality rate for the poorly treated group was 1.37 times that of the well-treated group in patients with aneurysm; 2.62 times as great in those with aortic insufficiency; and 2.02 times as great for the group as a whole.

6. The deaths due to cardiovascular syphilis were 1.62 times as great in the poorly treated as in the well-treated patients with aneurysm; 2.46 times as great in those with aortic insufficiency; and 2.06 times as great for the whole group.

7. Seventy patients of the series are dead.

8. The duration of life from onset of symptoms for those dead was 1.47 times as great in the well-treated as in the poorly treated patients for the whole group; 1.71 times as great in those with aneurysm; and 1.37 times as great in the patients with aortic insufficiency. The latter figure is not of certain statistical significance.

9. A restudy of Grant's cases of syphilitic aortic insufficiency was made.

10. The mortality rate of his poorly treated group was 1.35 times that of those well treated; deaths due to cardiac disease were 1.78 times as frequent in the former as in the latter.

11. No significant difference in the duration of life in his two groups was observed.

CONCLUSIONS

Properly directed antisyphilitic therapy results in a prolongation of life in two-thirds of the patients with saccular aortic aneurysm or syphilitic aortic insufficiency. The remaining third come under observation with an initially bad prognosis and do not survive sufficiently long for proper therapy to be administered.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION

IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery* †

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In previous articles of this series we have had occasion to refer to certain peculiarities in the form of the RS-T segment and T deflection observed in direct leads from the peripheral portions of subacute infarcts induced by ligation of the anterior descending branch of the left coronary artery. We have mentioned the characteristic modifications of the QRS deflections frequently seen in the same leads and also in leads from regions where only the inner layers of the ventricular wall are infarcted. Finally, we have commented upon the resemblance between the ventricular complexes inscribed in leads from infarcted portions of the ventricular wall which are no longer responding to the excitatory process and those obtained by introducing the exploring electrode into the cavity of the left ventricle. It is our present purpose to describe experiments in which more extensive observations relating to these phenomena were carried out, and to discuss their significance.

The methods employed in our experiments have been fully described in previous articles.[1, 2, 3] We may again point out that all direct and semidirect leads were taken simultaneously with standard Lead I and with a vacuum tube in the galvanometer circuit. The exploring electrode was paired with an electrode of the same type placed in contact with the subcutaneous tissues of the left (occasionally of the right) hind leg.

For the purpose of determining whether the subepicardial muscle in a given region was living or dead, we made extensive use of a sharp electrode, which consisted of a short length of enameled copper wire sharpened at one end, where the insulation was scraped off for a distance of one or two millimeters. The form of the ventricular complexes obtained when such an electrode is pressed against the surface of the heart has been described elsewhere.[5] When the subepicardial muscle is dead, the curve obtained is identical with that recorded by means of

*For previous articles of this series see Wilson, Hill, and Johnston,[1, 2] and Johnston, Hill, and Wilson[3]. The observations reported in this article were briefly described in a paper read at a recent meeting of the Association of American Physicians[4].

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a soft-tipped electrode of the ordinary type. In the article referred to, it was pointed out that, when this muscle is normal, a reduction in the height of the intrinsic deflection and pronounced downward displacement of the RS-T segment results, but the form of the preintrinsic portion of the ventricular complex is not altered. This principle is illustrated exceptionally well by the curves of Figs. 5 and 6 of this article.

ILLUSTRATIVE EXPERIMENTS

Experiment I (Dog 44).—In this instance the electrocardiographic observations were begun about twelve hours after ligation of two large subdivisions of the anterior descending branch of the left coronary

Fig. 1—Experiment I (Dog 44). Photograph of the left anterolateral surface of the heart showing the location and extent of the infarcted region.

artery. The chest had been carefully restored immediately after the ligation operation, and, before it was again opened, the standard leads and a set of three precordial leads were taken.. The standard curves showed conspicuous upward displacement of the RS-T segment in Leads II and III and slight upward displacement of this segment in Lead I. Distinct, but not abnormally large, Q deflections were present in all three leads. The precordial leads were taken by pairing a copper disk (about one inch in diameter and fitted with a suitable binding post) sewn beneath the skin with an indifferent electrode on the right hind leg. Three such disks were arranged along a line which made an angle

of about 40 degrees with the long axis of the body. The first was placed in the midline and yielded a curve in which the QRS group began with a small downward movement. The second was placed 6 cm. and the third 12.5 cm. to the left of the midline. Both yielded curves in which the first and most prominent deflection of the QRS group was upward. The T deflection was sharply inverted in all three curves.

When the heart was exposed, the infarct appeared as a large hemorrhagic area on its left anterolateral margin. This area was roughly elliptical; its greater diameter measured about 5 cm. and its smaller diameter about 4 cm. (Fig. 1). At the end of the experiment the heart was sectioned, and it was found that, in the central portions of the region affected, the infarct extended completely through the ventricular wall. Near the margins of this region the involvement was patchy. On

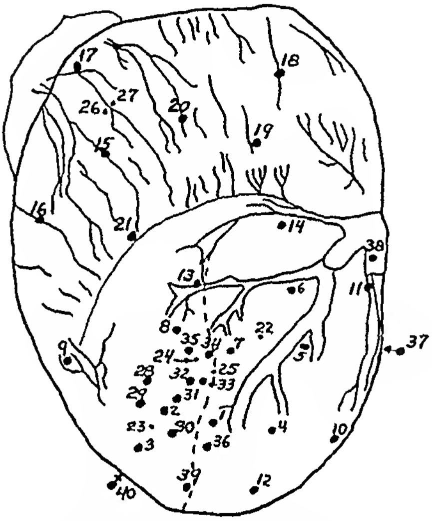

Fig. 2.—Experiment I (Dog 44). Outline drawing of the anterior surface of the heart showing the location of the points from which direct leads were taken. The broken line marks approximately the right border of the infarct.

the endocardial surface the limits of the infarct were rather poorly defined, but the area involved appeared to be approximately as large as on the outer surface.

The points from which direct leads were taken are indicated on an outline drawing of the anterior surface of the heart shown in Fig. 2, and samples of the curves obtained are reproduced in Fig. 3. The curves from points *9, 15, 16, 17, 18, 19, 20, 21,* and *40,* all outside the boundaries of the infarcted region, are of the type usually obtained from corresponding points on the surface of the undamaged heart.[5] The QRS group begins with a conspicuous downward movement, which is immediately followed by the intrinsic deflection, a sharp upstroke of large amplitude represented by a thin, barely visible line. A sharp exploring electrode pressed against the ventricular wall at point *26* yielded a curve in which QRS and T are completely fused. The descending

limb of this monophasic curve is interrupted by a notch which marks the position of the intrinsic deflection abolished by the injury. A curve obtained from the cavity of the right ventricle at point *27* shows a small preliminary downward movement followed by a tall summit; the RS-T segment and T are represented by a deep U-shaped depression.

The curves from the central portion of the infarcted region (points *4, 5, 6, 10, 11, 12,* and *37*) are similar to those obtained from the infarcted region in the experiments described in the third article[2] of this series. The ventricular complex is essentially diphasic and consists of a tall initial summit followed by a rounded depression, which, in some instances, ends with a small elevation above the base line. In the curves from points *5, 10, 11,* and *12* the initial summit is the sole deflection of the QRS group, and there is no trace of a true intrinsic upstroke. Curves of almost identical contour were obtained by thrusting a sharp electrode first into the wall and later into the cavity of the left ventricle at point *22.* We may conclude that at these points the ventricular wall was dead and was not responding to the excitatory process.

In the curve from point *4* the descending limb of the chief deflection dips below the base line, and there is an upward movement about one millimeter before the gradual slope of the RS-T segment begins. In the curve from point *6,* which is similar, the amplitude of the upward movement varies rhythmically between 0.5 cm. and 9 mm. Similar variations in the form of the ventricular complex are seen in the curves from several points. They are apparently due to slight to-and-fro movements of the exploring electrode caused by rhythmic inflation of the lungs. In the curves from points *37* and *38* there is a small but sharp upstroke which produces a conspicuous notch on the descending limb of the rather low initial summit. It is probable that these upstrokes represent intrinsic deflections of very small amplitude.[2]

The curves from the other points investigated, which were on or near the marginal portions of the infarcted region, are more difficult to describe. They vary greatly in form, and many of them show rhythmic variations of the kind already mentioned in the shape of the ventricular complex. As a class, these curves are characterized by the presence of both an abnormally tall initial summit and a conspicuous intrinsic upstroke. Many of them also display final deflections of unusual contour.

The curves from points *13* and *34* and some of the complexes of the curve from point *39,* however, are exceptions to this rule. The QRS group consists of a single tall upward deflection, and the intrinsic upstroke, if it is present, cannot be identified. In the first of these curves T is inverted; in the third it is sharply upright and of large amplitude; in the second a depressed RS-T segment is followed by a sharp upstroke which rises well above the zero level.

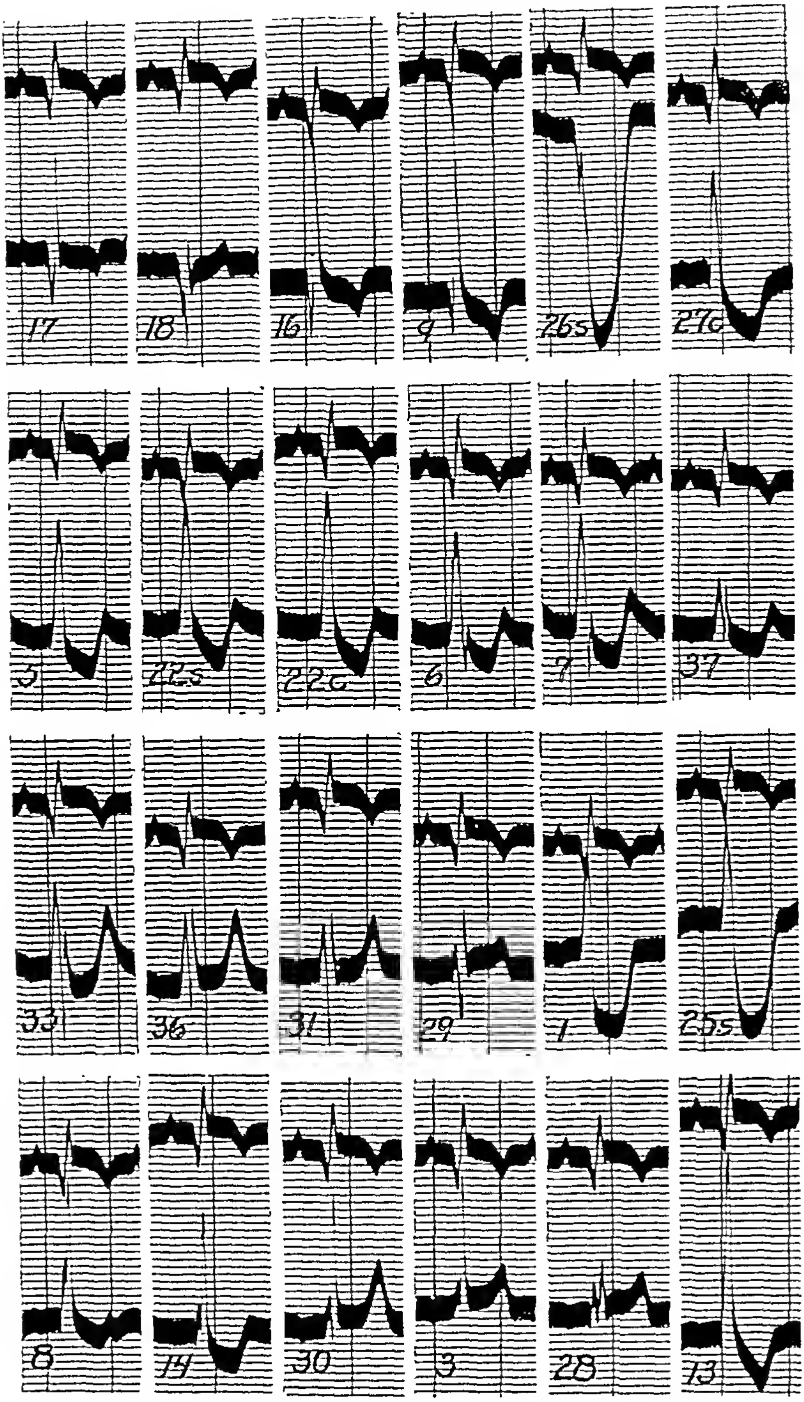

Fig. 3.—Experiment I (Dog 44). Direct leads from the points marked with corresponding numbers in Fig. 2. The letter *s* indicates that a sharp electrode was used and was pressed against the epicardial surface. The letter *c* indicates that the sharp electrode was pushed through the ventricular wall into the ventricular cavity. The upper curve in all records is standard Lead I. In taking direct leads, the connections were so made that relative negativity of the exploring electrode is represented by an upward deflection, and the galvanometer was adjusted to give a deflection of 1 cm. for a potential difference of 20 mv.

The remaining curves differ chiefly in respect to the height of the initial summit, to the amplitude of the intrinsic upstroke, to the magnitude of the downward movement that separates these two deflections, and to the character of the RS-T segment and T deflection. The curves from points *2, 7, 31, 32, 33* and *36* are very much alike and have a very characteristic outline. The upward movement at the beginning of the QRS interval is large, but the downward excursion which follows it is larger and in most instances carries the string shadow well below the base line. The downward movement ends with the onset of the intrinsic upstroke, which is represented by a very thin line and is of moderate amplitude. The RS-T segment is flat or depressed and T is sharply upright and in most instances exceptionally tall.

In the curve from point *1*, which is close to and between points *33* and *36* and might be expected to yield a similar curve, the tall initial summit and the large downward movement are present, but there is no intrinsic upstroke and the RS-T segment is displaced downward nearly a centimeter. The peculiarities of this curve are undoubtedly due to injury effects induced by pressing the exploring electrode too firmly against the heart. A curve of strikingly similar outline was obtained at point *25* (very close to point *33*) by thrusting a sharp electrode into the superficial layers of muscle.

In the curves from points *29* and *30* the initial upward movement is no larger than that sometimes seen in normal epicardial curves, and, although the curve from the former point resembles the curves under consideration in general outline, it cannot be considered definitely abnormal. The curve from the latter point shows rhythmic variations in form which affect the depth of the downward movement and the shape and height of T. In some complexes the downward movement crosses the base line, and T is very tall and is preceded by a flat RS-T segment; in others it fails to cross the base line, and T has a more normal shape. The curve obtained by pressing a sharp electrode against the muscle at point *23*, which is between points *29* and *30*, is similar to that obtained in the same way at point *25*, but the upward movement is smaller and in some complexes is preceded by a small excursion downward. A mere trace of a similar initial downward movement is visible in some of the complexes of the curve from point *29*.

In the curve from point *28* the initial upward movement is small. The downward excursion which follows it barely crosses the base line, and the succeeding upstroke is slow and of small amplitude. The T deflection shows rhythmic variations in form; in some complexes it is unusually tall but not peculiar in other respects.

The curves from points *8* and *35* are characterized by the smallness of the downward movement which separates the initial summit and the onset of the intrinsic upstroke. In many of the complexes this downward movement is absent, and the junction of the initial summit and

TABLE I

MEASUREMENTS OF THE CURVES OF EXPERIMENT I (DOG 44)*

POINT	VOLTAGE OF INITIAL SUMMIT	LEVEL OF INTRINSIC ONSET	TIME OF INTRINSIC ONSET	AMPLITUDE INTRINSIC DEFLECTION	RANGE OF FINAL DEFLECTION	
9	–	9.6	0.010	60.0	11.6	0.0
15a	–	8.0	0.020	41.6	8.0	– 4.0
15b	–	4.0	0.015	32.2	10.0	– 1.6
16	–	10.0	0.008	42.0	6.4	0.0
17a	–	4.0	0.022	31.6	4.0	0.0
17b	–	6.0	0.025	26.0	2.8	0.0
18a	–	22.0	0.031	27.4	2.0	– 4.6
18b	–	31.6	0.034	41.0	3.0	– 5.4
19a	–	7.0	0.027	9.6	15.6	– 1.8
19b	–	12.4	0.023	45.4	6.0	– 6.2
20a	–	13.4	0.022	25.6	9.2	0.0
20b	–	8.0	0.018	25.0	10.6	0.0
21	–	4.0	0.009	53.6	12.6	0.0
40	–	19.0	0.019	47.2	0.0	– 4.0
5	–28.0	–	–	–	8.6	– 4.1
10	–21.8	–	–	–	14.0	– 2.0
11	–12.0	–	–	–	6.0	– 3.0
12a	–21.6	–	–	–	11.0	– 1.6
12b	–30.0	–	–	–	16.0	0.0
4	–28.0	8.3	0.048	3.4	12.0	– 2.0
6a	–24.0	4.8	0.037	2.8	7.2	– 4.2
6b	–24.0	10.0	0.042	17.4	6.0	– 4.8
37a	–10.8	2.0	0.028	10.8	4.0	– 4.4
37b	–12.8	–1.2	0.030	2.0	4.0	– 4.4
38a	–10.0	–6.4	0.026	6.0	5.4	– 3.6
38b	– 6.0	2.2	0.027	6.0	2.8	– 3.6
13	–46.4	–	–	–	12.0	0.0
34a	–35.6	–	–	–	4.0	– 9.0
34b	–22.8	–	–	–	9.4	– 5.0
2	–13.8	16.0	0.032	30.0	1.6	–10.0
7a	–24.0	20.0	0.044	30.0	6.0	– 8.8
7b	–26.0	12.4	0.042	13.6	8.4	– 8.6
31	– 9.0	20.0	0.031	34.1	2.0	–11.0
32	–14.2	23.0	0.036	31.6	4.0	–13.4
33	–19.6	18.0	0.038	26.0	7.2	–14.0
36a	–14.0	14.0	0.036	34.0	–4.0	–20.0
36b	–17.2	3.8	0.034	20.0	–2.0	–18.0
1	–23.0	–	–	–	21.2	– 1.8
29a	– 4.0	14.0	0.033	29.4	–4.0	–10.6
29b	– 3.4	9.6	0.029	24.0	–3.2	– 6.0
30a	– 3.8	0.0	0.026	32.8	–2.0	–10.6
30b	– 7.6	9.6	0.031	36.0	–2.0	–15.6
28a	– 6.4	0.0	0.031	12.0	–3.0	– 8.0
28b	– 6.0	4.0	0.033	18.0	4.0	–14.6
8a	–15.4	– 6.0	0.023	30.6	4.8	0.0
8b	–15.4	–15.4	0.022	24.0	4.0	0.0
35a	–12.0	– 2.0	0.015	29.0	4.0	– 9.4
35b	–14.4	–14.4	0.020	22.0	1.6	– 4.0
14	– 2.8	– 2.8	0.019	27.0	6.8	– 1.6
39a	– 4.0	– 2.0	0.019	40.8	2.6	– 5.0
39b	–10.0	–10.0	0.019	24.0	1.6	–12.8
3a	– 3.6	– 2.0	0.019	33.0	–2.2	– 8.3
3b	–	10.0	0.017	46.0	0.0	– 2.0

*Voltages are expressed in millivolts, and time in seconds.

the intrinsic upstroke is represented by a notch or node on the ascending limb of the chief deflection. In other complexes the downward movement amounts to several millimeters.

The curve from point *14* and most of the complexes of the curve from point *39* are similar to these just mentioned, but the initial upward movement is smaller, and its junction with the intrinsic deflection occurs, therefore, at a lower level. Most of the complexes of the curve from point *3* are of the normal type, but there are rhythmic variations, and a few resemble those just described.

Since space is not available for the reproduction of all the epicardial curves taken, they have been carefully measured. The measurements are incorporated in Table I, which gives the height of the initial summit, the level with reference to the base line at which the intrinsic upstroke begins, the amplitude of this upstroke, the range of the RS-T segment and T deflection in millivolts, and the time of the intrinsic upstroke with reference to the earliest ventricular deflection in standard Lead I in seconds. The range of the final deflections is given by two figures; the first gives the potential level of the first turning point, the second, the potential of the second turning point when such a point exists. Since the galvanometer connections were so made that relative negativity of the exploring electrode produced an upward movement of the string shadow, minus signs have been affixed to measurements which locate points above the base line, and ordinates which lie below this line are considered positive.

Experiment II (Dog 11).—In this instance the electrocardiographic study was made seventy-eight days after ligation of the anterior descending branch of the left coronary artery. The standard electrocardiogram taken at this time does not strongly suggest the presence of an infarct. Conspicuous Q deflections and inverted T-waves are present in all three leads. Three precordial leads were also taken. The copper disks which served as the exploring electrodes were sewn beneath the skin along a line which made an angle of about 30 degrees with the long axis of the body. The first of these disks was placed in the midline, the second 6 cm., and the third 12 cm. to the left of this line. The indifferent electrode was placed on the left hind leg. In the first and second precordial curves QRS begins with a downward excursion; in the third the initial movement is upward but small. These curves cannot be considered as characteristic of myocardial infarction. When the heart was exposed, an extensive, discolored, and somewhat depressed area was found on its anterior surface. In the center of this region the pericardium was adherent. Later examination showed that in the immediate neighborhood of the adhesions the infarct penetrated the ventricular wall over an area about one centimeter in diameter. The histological examination (carried out by Dr. C. V. Weller) of a block of tissue removed from this region showed an old fibroid scar which except for a few muscle fibers (probably Purkinje tissue) on the endo-

cardial side extended completely through the ventricular wall. The section also showed phagocytes containing old blood pigment, mucoid change in the scar tissue, early metaplasia of this tissue to cartilage,

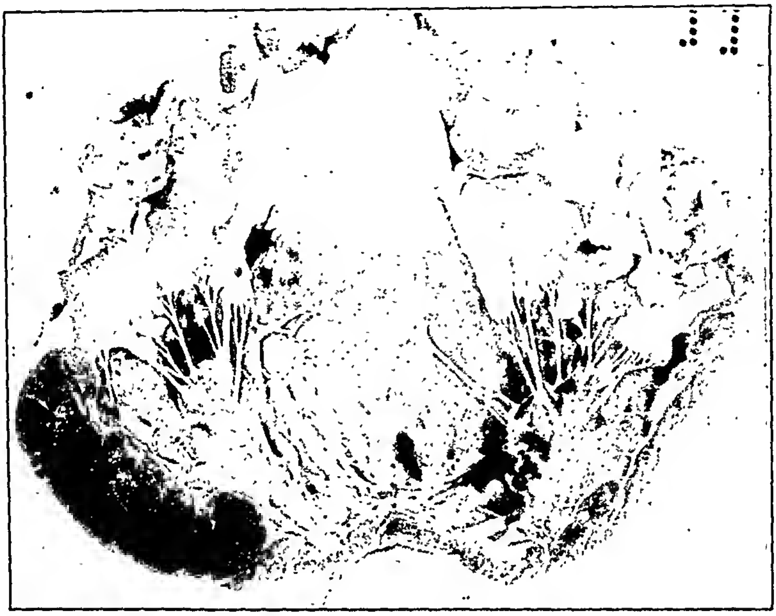

Fig. 4.—Experiment II (Dog 11). Photograph of the endocardial surface of the left ventricle.

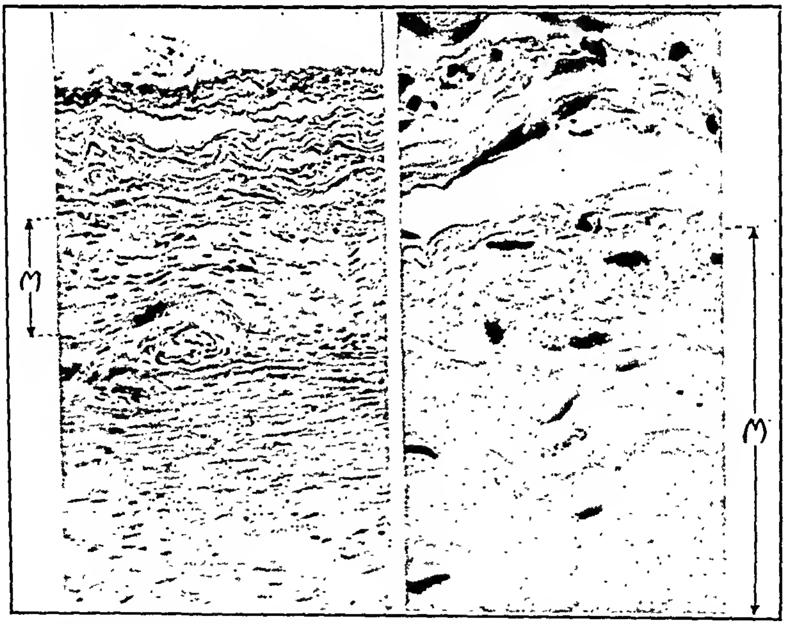

Fig. 5.—Experiment II (Dog 11). Photomicrograph of a section of the ventricular wall in the infarcted region. A thin layer of muscle fibers (*M*) lying just beneath the endocardium has escaped destruction. Low power on the left, and higher power on the right.

and small areas of lime deposit. A photograph of the endocardial surface of the left ventricle is reproduced in Fig. 4. It shows an extensive area of subendocardial fibrosis, which on the cut surface is seen to

involve the inner third or more of the ventricular wall. A photomicrograph of the section referred to is reproduced in Fig. 5.

Direct leads were taken from the points indicated on an outline drawing of the anterior surface of the heart shown in Fig. 6. Samples of the curves obtained are reproduced in Fig. 7.

The curves from points *9, 10, 11, 12, 13, 14, 15,* and *18* are of the normal type. The QRS group begins with a conspicuous downward movement which is immediately followed by an intrinsic upstroke of large amplitude, and the final portion of the ventricular complex has a normal contour. The curve from point *10* is very similar in general outline to that obtained at point *11,* but the initial downward movement is much smaller and amounts to less than 1 mm. At points *21* and *22* a sharp exploring electrode abolished the intrinsic deflection and yielded a purely monophasic response. At point *28* it gave a curve

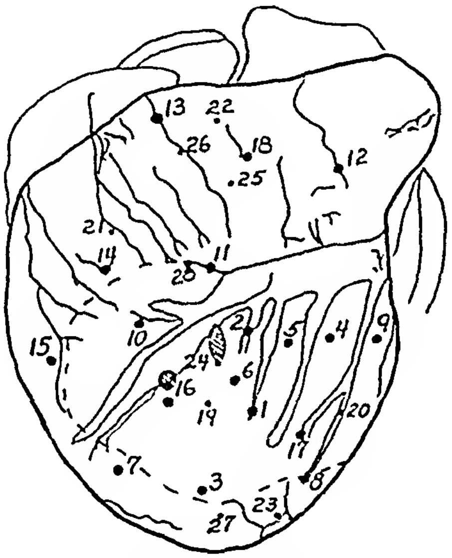

Fig. 6.—Experiment II (Dog 11). Outline drawing of the anterior surface of the heart showing the location of the points from which direct leads were taken. The crosshatched areas mark the location of pericardial adhesions. The broken line marks the limits of the discolored and depressed area mentioned in the text.

which, when compared with that obtained with the ordinary sponge-tipped electrode at nearby point *11,* shows a considerable decrease in the height of the intrinsic upstroke and a pronounced downward displacement of the RS-T segment. At point *10,* the changes in the ventricular complex induced by the sharp electrode were in the same direction but very small.

The curve from point *2,* where the infarct penetrated completely through the ventricular wall, is diphasic and consists of a tall unnotched initial summit followed by an inverted T deflection. There is no trace of an intrinsic upstroke, and no change whatever in the form of the ventricular complex occurred when the sharp electrode was employed. Curves of the same kind were obtained when this electrode was thrust into the left ventricular cavity at point *24* and at point *27.*

So far as the form of the QRS deflections is concerned, the curves from points *1, 3, 4, 5, 6, 7,* and *8* resemble those obtained from the

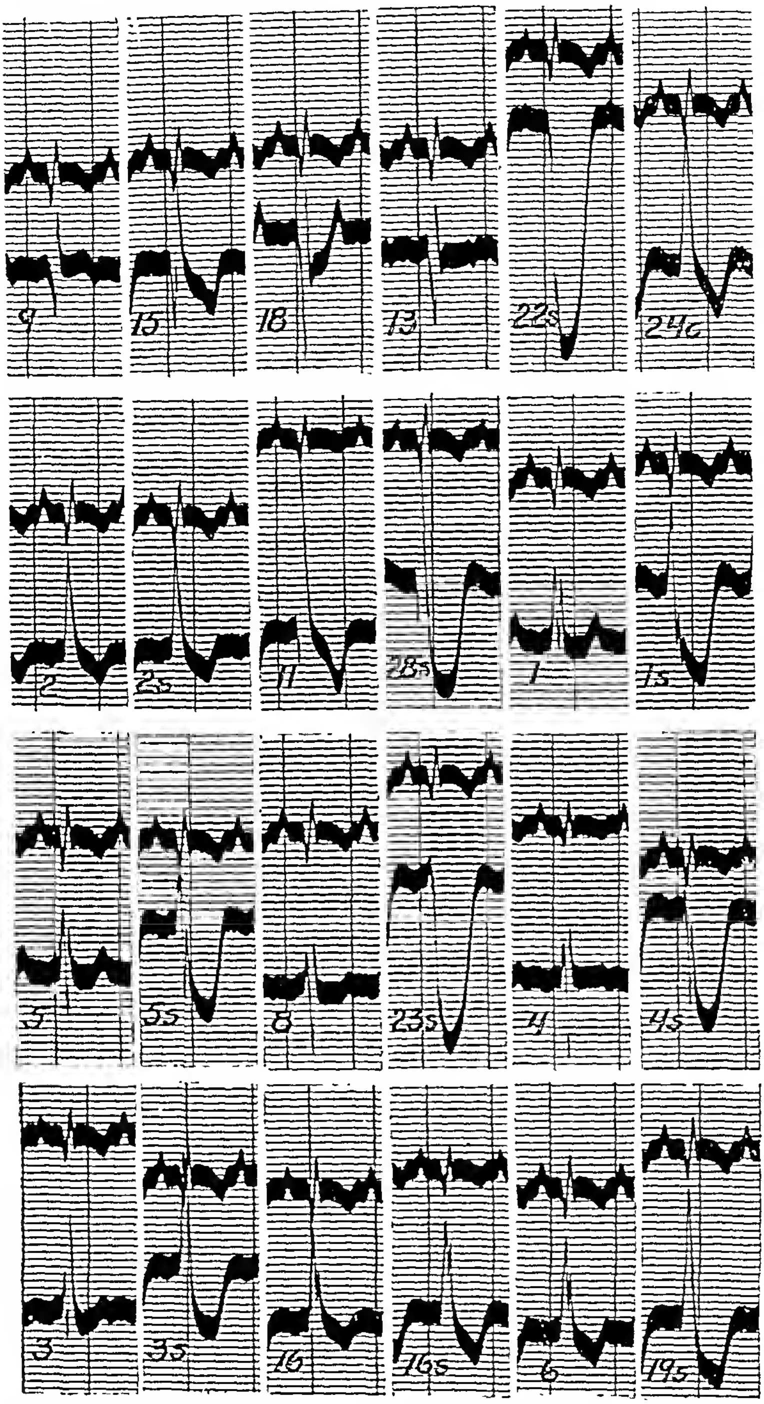

Fig. 7.—Experiment II (Dog 11). Direct leads from the points bearing corresponding numbers in Fig. 6. The upper curve in all records is standard Lead I. The conventions and additional data are the same as in the case of Fig. 3.

marginal portions of the infarcted region in Experiment I. They display both an initial summit and an intrinsic deflection and differ only

in respect to the size of these deflections and to the magnitude of the downward movement that separates them. The RS-T segment and T deflection, however, show no unusual features. At the majority of these points the injury inflicted by using a sharp electrode had no appreciable effect upon the preintrinsic portions of the ventricular complex. The intrinsic upstroke was reduced in height or abolished, and the postintrinsic deflections were converted into a deep U-shaped depression. At points *3* and *7* and at point *19,* which is near point *6,* the curves obtained with the sharp electrode are exceptions to this rule. Except for the greater depression of the final portions of the ventricular complex, they resemble those obtained from the cavity of the left ventricle. It is possible that at these points the sharp electrode penetrated the living muscle and reached the layer of scar tissue beneath. The orig-

TABLE II

MEASUREMENTS OF THE CURVES OF EXPERIMENT II (DOG 11)*

POINT	VOLTAGE OF INITIAL SUMMIT	LEVEL OF INTRINSIC ONSET	TIME OF INTRINSIC ONSET	AMPLITUDE INTRINSIC DEFLECTION	RANGE OF FINAL DEFLECTION	
9	–	12.6	0.022	27.4	–1.8	0.0
10	–	2.6	0.003	47.2	15.0	0.0
10s	–	1.2	0.003	42.5	19.6	0.0
11	–	8.0	0.003	49.0	15.0	0.0
28s	–	6.0	0.003	40.0	30.0	–2.6
12	–	6.4	0.017	26.0	5.0	–0.8
13	–	20.0	0.020	28.6	4.6	0.0
14	–	13.8	0.005	50.0	14.0	0.0
15	–	15.6	0.007	52.8	12.0	0.0
18	–	34.0	0.021	41.6	13.6	–5.0
21s	–	–	–	–	55.0	0.0
22s	–	–	–	–	61.4	0.0
2	–25.0	–	–	–	6.0	0.0
2s	–26.0	–	–	–	7.0	0.0
24c	–33.0	–	–	–	11.2	–1.6
27c	–33.0	–	–	–	14.4	–0.6
1a	–17.2	1.0	0.022	14.0	2.0	–4.0
1b	–17.2	–1.6	0.020	14.0	2.0	–5.4
1s	–19.6	–	–	–	25.0	0.0
3a	– 5.6	12.4	0.018	34.0	3.6	–0.6
3b	– 7.0	6.0	0.020	32.0	5.0	0.0
3s	–24.0	–	–	–	18.0	0.0
4	– 6.0	20.0	0.022	29.6	1.0	0.0
4s	– 3.0	22.0	0.022	17.6	30.0	0.0
5	–14.0	11.0	0.025	18.4	2.0	–3.0
5s	–11.4	22.4	0.028	13.0	24.4	0.0
6	–23.0	9.4	0.023	7.0	6.0	–1.0
19s	–32.2	–	–	–	16.6	0.0
7	– 8.1	4.0	0.017	26.0	2.0	0.0
7s	–20.0	–	–	–	22.0	0.0
8	– 5.2	18.0	0.024	23.6	2.0	0.0
23s	– 4.0	–	–	–	47.2	0.0
16	–21.2	– 8.0	0.024	2.0	6.0	0.0
16s	–23.6	–11.2	0.021	4.4	11.6	0.0
17	– 3.6	14.0	0.023	21.6	5.2	0.0

*Voltages are expressed in millivolts, and time in seconds. When large rhythmic variations in the form of the ventricular complex occurred, the two complexes which differed most widely were measured. The two sets of measurements are designated by the letters *a* and *b*.

inal curve from point *16* shows a slight notch on the descending limb of the initial summit, but no other indication of the presence of an intrinsic deflection. The curve obtained with the sharp electrode shows only minor differences; the notch occurs at a slightly higher level, and T is somewhat more negative. It is, therefore, not certain that there was any living muscle at this point.

Measurements of the curves of this experiment are given in Table II.

COMMENT

The observations described show clearly that, when the whole thickness of the left ventricular wall is made up of scar tissue or dead muscle, the potential variations which occur at the epicardial surface of the region affected and those that take place in the neighboring portions of the ventricular cavity are practically identical. The potential variations occurring in the left ventricular cavity vary from point to point, but the general course of events is everywhere the same, and the curves obtained by leading from the epicardial surface of infarcts that extend completely through the left ventricular wall have, therefore, a characteristic outline. The initial and sole deflection of the QRS group is a tall summit, and T is usually inverted. There is no trace of a sudden intrinsic upstroke such as occurs in epicardial leads from healthy muscle.

It is apparent that, when the ventricular complexes recorded by leading from the epicardial surface and those obtained by leading from the nearest portion of the ventricular cavity are strikingly different, we may conclude that the intervening section of the ventricular wall is made up in whole or in part of muscle that is alive and is responding to the excitatory process. The electric forces generated by this muscle must be responsible for all the major differences observed. By comparing the ordinates of the one lead with the corresponding ordinates of the other, the general character of the time course of these electrical forces may be determined.

At the great majority of points on the anterior surface of the normal left ventricle, the potential with respect to an indifferent point becomes positive at the very beginning of the QRS interval, and this initial positivity increases more or less uniformly throughout the preintrinsic period. Since the ventricular cavity undergoes potential variations of the opposite kind at the onset of systole, it is evident that by far the greater part of the subendocardial muscle on the anterior wall of the left ventricle is already passing into the excited state when the QRS interval begins and that throughout the first part of this interval the electrical forces produced by the inner layers of muscle rapidly increase in magnitude. During this period the positivity of the epicardial sur-

face can continue to increase only as long as the growth of these forces is more rapid than the growth of negativity in the ventricular cavity. Later, when the inner negativity has reached its maximum and has begun to decline, the potential of the epicardial surface must rise unless the electromotive force across the ventricular wall is rapidly decreasing. When the excitation wave arrives at the epicardial surface in a given region, the electrical forces generated by its spread through that section of the ventricular wall are abruptly extinguished. The sudden decrease in the positivity of the epicardial surface thus brought about is represented in direct leads by the intrinsic deflection. The post-intrinsic QRS deflections of epicardial leads are similar to those inscribed during the same period in leads from the ventricular cavity.

It has been pointed out that the QRS group of many of the curves described displays both a prominent initial summit and a conspicuous intrinsic upstroke. The presence of the latter and the striking injury effects which appeared when a sharp electrode was pressed against the epicardial surface indicate that, in the regions from which these curves were obtained, the outer layers of muscle were alive and were responding to the excitatory process. During the inscription of the prominent initial summit the potential of the epicardial surface was negative and not, as a rule, materially different from that of the ventricular cavity. The presence of this deflection shows, therefore, that the innermost layers of muscle either produced electrical forces of subnormal magnitude or were activated abnormally late. In all probability both factors were operative, and we shall not attempt to reach a final decision as to which was the more important. The small initial summit which is not infrequently seen in direct leads from certain parts of the anterior surface of the normal heart is almost always followed by a large downward movement and a relatively late intrinsic deflection, and may logically be ascribed to late endocardial activation. In the case of the much larger initial summits under consideration, however, the situation is somewhat different. Very late activation of the endocardial surface should lead to equally late activation of the epicardial surface and should delay greatly the onset of the intrinsic upstroke. In some of the curves in question this deflection may be slightly delayed, but it does not appear to be greatly delayed in any. In many of these curves the downward movement which follows the initial summit is large and crosses the base line, whereas in others it is small or absent. It should be noted that in the former the intrinsic upstroke occurs relatively late while in the latter it is usually early. In the first case it usually begins after; in the second, before the negativity of the ventricular cavity has reached its maximum. It is obvious that a given rate of increase in the electromotive force across the ventricular wall will be much more likely to produce a downward movement when the negativity of the ventricular cavity is declining than when it is increasing.

In several experiments we attempted to determine whether section of the anterior subdivision of the left branch of the His bundle is followed by the appearance of an initial summit in direct leads from those portions of the ventricular surface to which it distributes the excitation wave. On the whole, these experiments were not very successful. In one or two instances a small initial summit appeared in a lead in which the QRS group originally began with a downward movement, or an initial summit originally present became slightly larger. None of the curves obtained displayed an initial summit large enough to be recognized at once as abnormal.

It is evident that in Experiment II curves of the kind in question were obtained only from those regions where the subendocardial muscle had been replaced by scar tissue and the subepicardial muscle was still living. Similar observations were made in other instances in which only the inner layers of muscle were infarcted. In such cases there is no reason to doubt that the magnitude of the electric forces produced by the subendocardial muscle were subnormal in magnitude. In Experiment I the muscle changes had not progressed far enough to enable us to determine easily the exact distribution of the infarcted tissue. The curves from points near the margin of the infarct are, however, strikingly similar to those obtained from regions where only the inner layers of muscle were involved in other experiments, and it does not seem probable that they had a different origin.

The observations made in Experiment II, and other experiments of a similar kind, present a very perplexing problem. Since the excitatory process spreads from the endocardial surface outward, it is difficult to see how it can reach the outer layers of muscle when the inner layers are dead or have been replaced by scar tissue. It is conceivable that it might reach this muscle by way of the normal parts of the ventricular wall beyond the boundaries of the subendocardial lesion, but this would require a great deal of time and must greatly delay the onset of the intrinsic deflection in the region affected. Since the intrinsic deflection is not greatly delayed, it would seem that the excitatory process must pass through the dead muscle or scar tissue, as the case may be. In this connection it is interesting that in Experiment II histological examination of the infarcted region showed that a thin layer of muscle fibers immediately beneath the endocardium was still intact. Dr. B. S. Oppenheimer was good enough to examine the sections which show these fibers and expressed the opinion that they were part of the Purkinje plexus. It is well known that Purkinje tissue tolerates oxygen want better than ordinary muscle, and this circumstance, together with the position of the left Purkinje plexus in relation to the blood of the left ventricular cavity, may explain its preservation in cases of the kind under consideration. Granting that much of the Purkinje network escapes in subendocardial infarcts, we are still unable to understand how

the excitatory process can cross the infarcted tissue unless we suppose that this tissue is penetrated by living Purkinje fibers or by surviving strands of ordinary muscle.

The flat or depressed RS-T segment and exaggerated T deflection encountered in direct leads from the margins of subacute infarcts of the left ventricle are obviously analogous to the so-called "coronary T-wave" seen in human coronary occlusion. In man these changes in the final portion of the ventricular complex may appear early, but they often reach the height of their development ten days or more after infarction occurs. In our animal experiments, on the other hand, they were never seen to persist in direct leads as long as twenty-four hours after coronary ligation. The reason for this difference between clinical and experimental myocardial infarction is not apparent.

While the flat or depressed RS-T segment may be a remnant of the injury effects that occur in the earliest stages of infarction, the T-wave changes are clearly due to disturbances that affect the return of the muscle from the active to the resting state. Since they are transient they cannot, like the QRS changes, be attributed to the disappearance of electrical forces normally produced by muscle that has been killed but must depend upon the generation of abnormal electrical forces in muscle that has been damaged. In leads from the ventricular cavity the final portion of the ventricular complex is usually represented by a U-shaped depression, which may be followed by a slight elevation above the base line. The occurrence of abnormally tall upright T deflections in epicardial leads indicates, therefore, that the magnitude of the electrical forces generated late in systole by the corresponding parts of the ventricular wall is abnormally great. The polarity of these forces is such as to make the epicardial surface negative, and it is possible that in the region affected the duration of the excited state increases from within outward. Smith[6] observed somewhat similar changes in the T deflection of direct leads accompanied by an increase in the duration of electrical systole and the length of the absolute refractory period when the muscle beneath the exploring electrode was cooled to a low temperature.

The close association in epicardial leads of final deflections of the kind in question and QRS deflections of the type discussed in preceding paragraphs suggests that the former, as well as the latter, may be in some way dependent upon effects produced in regions where only the inner layers of muscle are infarcted.

Throughout this discussion we have attempted to analyze curves inscribed in direct leads from an infarcted region by comparing them with those obtained from neighboring parts of the ventricular cavity. We do not wish to give the impression that infarction of the ventricular wall does not influence the potential variations occurring in the ventricular cavity. Theoretical considerations indicate that it must modify

them, and particularly those taking place at the nearest points. It is difficult, however, to demonstrate experimentally that this is the case, for it is evidently the magnitude rather than the general character of these variations that is altered. Changes in magnitude are not easily recognized without adequate controls, and to obtain such controls it is necessary to return the exploring electrode to precisely the same spot in the ventricular cavity that it previously occupied, or to allow it to remain in place throughout the period of observation. Because of the technical difficulties this question has not been investigated.

SUMMARY

Direct leads from the surface of infarcts that extend completely through the left ventricular wall yield ventricular complexes practically identical with those obtained by leading from the neighboring parts of the ventricular cavity. When the galvanometer connections are so made that relative negativity of the exploring electrode produces an upward deflection, these curves consist of a tall initial summit followed by a U-shaped final deflection which sometimes ends with a slight elevation above the base line.

In direct leads from regions where the inner layers of muscle are dead or have been replaced by scar tissue and where the outer layers are still living and responding to the excitatory process, the QRS group is characterized by the presence of both an abnormally large initial summit and a conspicuous intrinsic upstroke. A pronounced downward movement usually separates these two deflections but may be absent.

In the subacute stages of infarction the RS-T segment is often flat or depressed and the T-wave upright and abnormally large in leads from the marginal portions of the infarct. These changes in the final portion of the ventricular complex are usually associated with QRS deflections of the kind observed when only the inner layers of muscle are involved. Unlike these QRS changes, they persist for a very short time. They are due to disturbances affecting the recovery process in muscle that has been damaged, and not to the disappearance of electrical forces normally produced by muscle that has been killed.

We owe our thanks to Dr. John Nyboer, who made the measurements given in Tables I and II and to Dr. John Bugher, who was good enough to take for us the photomicrographs shown in Fig. 5.

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THE RELATION OF THE POSITION OF THE HEART TO THE INITIAL VENTRICULAR DEFLECTIONS IN EXPERIMENTAL BUNDLE-BRANCH BLOCK*

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ON THE basis of changes in the contour of experimentally produced canine bundle-branch block curves when the heart's position is altered, Ackerman and Katz[1] have recommended that no attempt be made to designate the bundle branch involved and that instead all such cases be called intraventricular block of the bundle-branch type. More recently Katz and his coworkers[2] have described two cases of left bundle-branch block (new terminology) in human beings in which changing the heart's position by altering the patient's posture resulted in electrocardiograms of an "indeterminate type."

We have repeated the experiments of Ackerman and Katz on thirteen dogs and two monkeys producing right block ten times and left block five times, displacing the hearts according to the technic of these authors and confirming the lesions by dissection. In confirmation of the above authors, we observed changes in the contour of the electrocardiograms including reversal in direction of QRS in Leads I or III, these changes being most easily produced by rotation of the heart on its long axis, simple displacement of the apex laterally or anteriorly being less effective. Typical results, using left branch block in the dog and monkey, are given in Fig. 1 and Fig. 2. Examples of reversal in Lead I and in Lead III are seen in each case.

The fact that right bundle-branch block in the dog gives curves, the initial deflections of which are typically inverted in all leads, and left branch block gives upward initial deflections in all leads, is now almost universally accepted. In exceptional cases the direction of the initial deflections may be oppositely directed in Leads I and III, or to use Lewis's terminology, the curves are "discordant." In Fig. 4 we have indicated by arrows the direction of the electrical axis in each of our experiments, and it will be seen that with right bundle-branch block "discordancy" occurred twice, once in Lead I and once in Lead III. All left bundle-branch curves were "concordant." Each of the monkeys, one with right and one with left block, gave "concordant" curves, thus being in agreement with the usual findings in the dog.

Although displacement of the heart by values equal to those used by Ackerman and Katz[1] altered the direction of the initial deflection at

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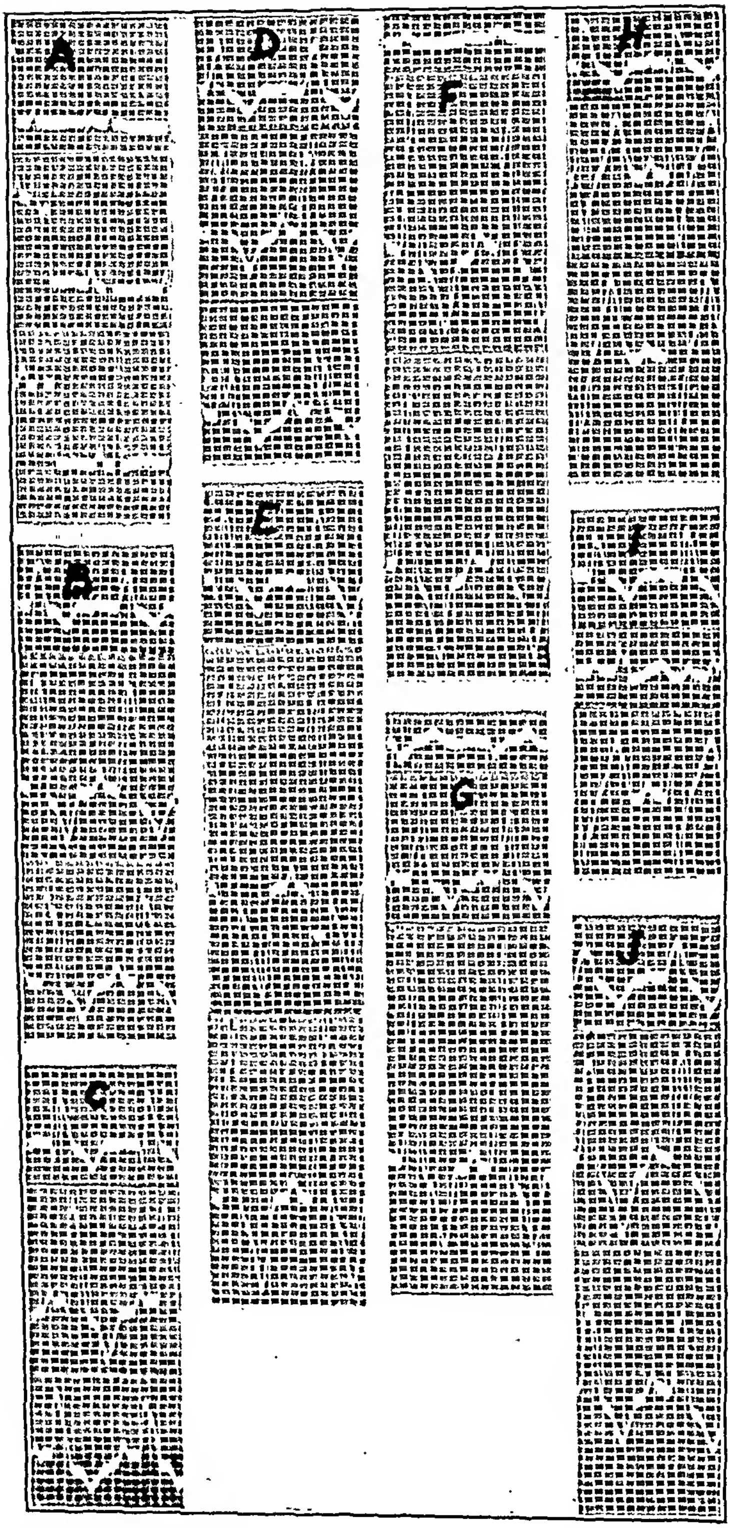

Fig. 1.—Effect of changing the position of the heart on the electrocardiogram in left bundle-branch block in the dog. (Curves in each block from top to bottom are Leads I, II, and III.)

A. Normal mechanism; chest open. B. After section of left bundle branch. Heart in normal position. C. Apex elevated 45°. D. Apex displaced left 30°. E. Apex displaced right 30°. F. Rotated left on long axis 30°. G. Rotated left 90° (as far as was possible). H. Rotated right 60° (as far as was possible). I. Rotated right 30°. J. Apex displaced left 30° and rotated left 30°.

times in Leads I or III in both right and left branch block, these curves simply became "discordant" curves of the same type and could hardly be confused with block of the opposite type. Fig. 4 shows the relation between the direction of the electrical axis and the direction of the initial deflections in each lead with the approximate range of human and canine branch block curves indicated. It is seen that the electrical

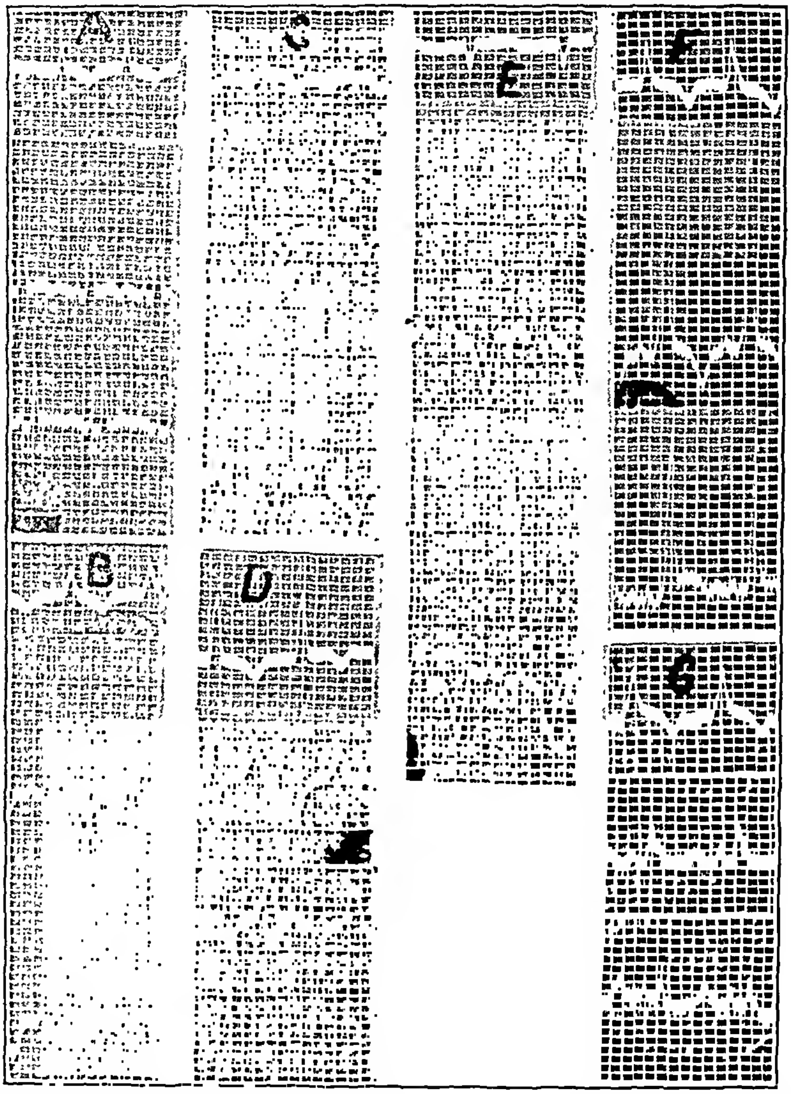

Fig. 2.—Effect of changing the position of the heart on the electrocardiogram of left bundle-branch block in the monkey. (Curves in each block from top to bottom are Leads I, II, and III.)

A. Normal mechanism; chest open.
B. After section of the left bundle-branch. Heart in normal position.
C. Apex elevated 45°.
D. Heart rotated right on long axis 45°.
E. Rotated left 45°.
F. Apex displaced right 30°.
G. Apex displaced left 30°.

axis must be displaced upwards of 180 degrees to change one type of curve into exactly that of the opposite type. That this is experimentally possible is illustrated in Fig. 3. In this case right bundle-branch block

with definitely downwardly directed complexes in all leads was made to resemble left bundle-branch block by displacing the apex until it pointed cephalad and rotating the heart so as to bring the right ventricle ventrad and the left dorsad as far as possible. Cardiac displacement of so ex-

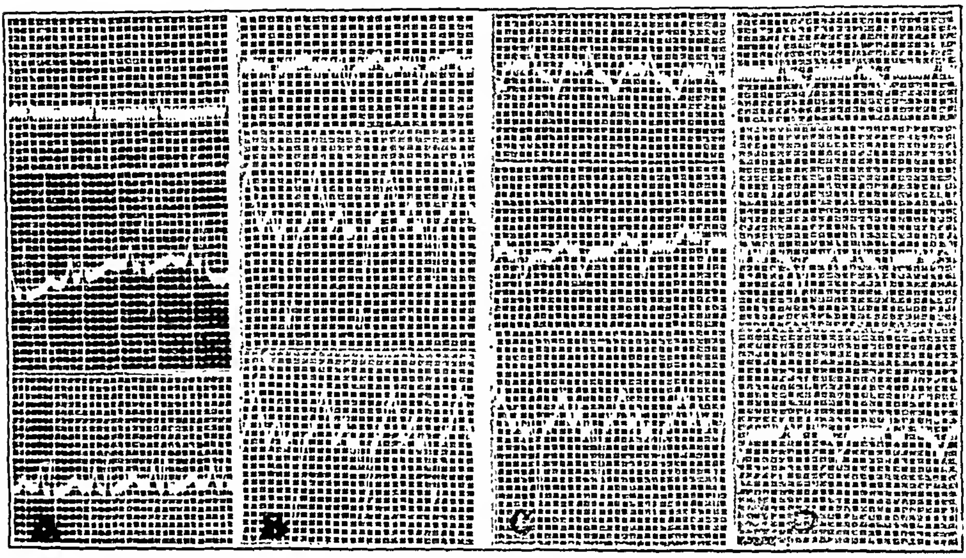

Fig. 3.—(Curves in each block from top to bottom are Leads I, II, and III.)
A. Normal mechanism. Chest open.
B. After section of the right bundle-branch.
C. Effect of displacing apex 15° upward, 30° to the left and rotating heart on the long axis 30° to the right.
D. Effect of completely inverting the position of the ventricles. Apex displaced anteriorly as far as possible, right ventricle rotated to left and left ventricle rotated to right as far as possible.

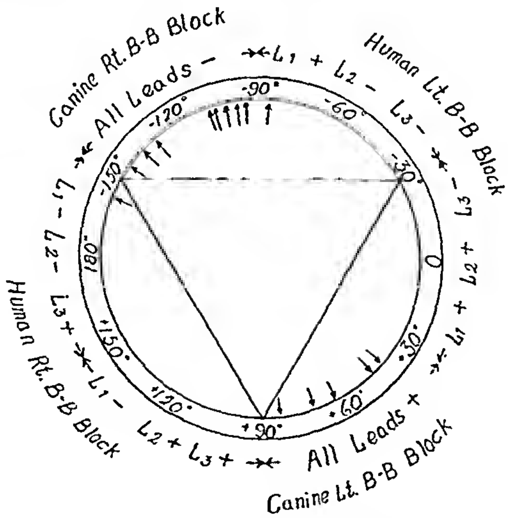

Fig. 4.—Relation between the direction of the electrical axis and the direction of the initial ventricular deflections in each of the standard leads. The small arrows indicate the direction of the axes in our cases of experimental branch block. The approximate range of axes in human and canine branch block is indicated.

treme a degree would be very unlikely to occur pathologically, and, if it did occur, it would hardly escape notice. We doubt if such experiments invalidate the use of the terms *right* and *left* bundle-branch block.

In the human cases cited by Kissin, Ackerman and Katz,[2] in which placing the patient on the left side resulted in the changing of curves from the type now generally considered to be typical of left bundle-branch block to an "indeterminate type," the electrical axis has been rotated to the right sufficiently that a downwardly directed wave in Lead III is now upwardly directed, but the axis still points left. We have seen the electrical axis in normal people rotate almost as much with changes of body position, but only in exceptional cases. That the position of the heart alters the contour of the waves in the electrocardiogram is no new idea, having been studied in Einthoven's laboratory[3] as early as 1913 and more extensively by Meek and Wilson[4] at a later date. Herrmann and Wilson[5] recognized that there must be fairly marked hypertrophy of a ventricle before a definite relation between the form of the ventricular complex and the relative weight of the two ventricles exists. Every electrocardiographer recognizes that with moderate axis deviation the body build of the patient as well as the body position while taking the record must be considered in evaluating such axis deviation. Thus, while admitting that alteration in the position of the heart may slightly modify the contour of the initial ventricular complexes, this, in most instances, we believe, would not lead to confusion in the bundle involved. In the two cases of Kissin, Ackerman, and Katz[2] the electrical axis at all times points so unmistakably to the left that on examining any of the curves the diagnosis of *left* bundle-branch block would appear to be the correct one.

SUMMARY

We see no valid experimental evidence that warrants the abandonment of the use of the terms *right* and *left* in describing intraventricular block of the bundle-branch type.

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THE ANATOMICAL AND HYDROSTATIC BASIS OF ORTHOPNEA AND OF RIGHT HYDROTHORAX IN CARDIAC FAILURE*

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THE accumulation of blood and edema fluid in the dependent parts of the lung is recognized as a common consequence of passive hyperemia due to heart failure and as a predisposing cause of terminal pneumonia and of hydrothorax. However, the hydrostatic analysis of pulmonary venous drainage has not been used in accounting for orthopnea and the preponderance of right-sided pleural transudates, although these phenomena have excited curiosity and experimental study leading to varied and often rather complicated explanations. Widely current theories ascribe right hydrothorax to the pressure of the right auricle on the right pulmonary vein, and orthopnea to postural facilitation of thoracic and diaphragmatic movement or to changes in vital capacity when blood shifts into the lungs from the dependent parts of the body. In this paper I shall discuss the gravitational relations of the pulmonary outflow to the left ventricle, and indicate that most of the blood reaching the left ventricle from the lungs must run uphill whenever the patient lies on his back or his right side, but that ventricular filling from the pulmonary bed is aided by gravity when the shoulders are elevated or when the patient is in the left lateral position. The relation of these facts to orthopnea and to the frequency of right hydrothorax is obvious, since venous pressure must be higher in order to force blood upward and high venous pressure causes more rapid transudation, leading both to pulmonary edema with impaired respiration and to pleural effusion.

METHODS

Data on the relation of the blood in the lungs to the left ventricle were obtained from a study of recorded drawings of cross-sections of the adult thorax and from roentgen ray films. The object of the measurements was to determine the geometric center of the left ventricular cavity and of the lungs, and the vertical distance between these two points in erect and supine positions.

The lung fields of two sets of cross-sections[1, 2] were copied on sheets of uniform thickness, and the skin surface behind was marked on each sheet. The center of the left ventricle was placed by inspection; its distance anterior to the skin surface measured; and this distance laid off on each sheet. Lines parallel to the line of support behind were drawn through the level of the center of the left ventricle and

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DISCUSSION

On inspection of the thoracic viscera of embalmed cadavers, of cross-sections, or of anteroposterior roentgen ray projections (Fig. 1) of the chest, it is evident that the center of the right lung lies nearly 10 cm. below the left ventricle in the right lateral recumbent position, and that of the left lung is only 2 to 5 cm. below the left ventricle in the left lateral position. Since cardiac patients, often conscious of the apex beat, tend to roll toward their right sides in order to rest their backs, it is only natural that throughout the day the pulmonary venous pressure on the right should average several centimeters of water more than the left. In left heart failure and in mitral stenosis,

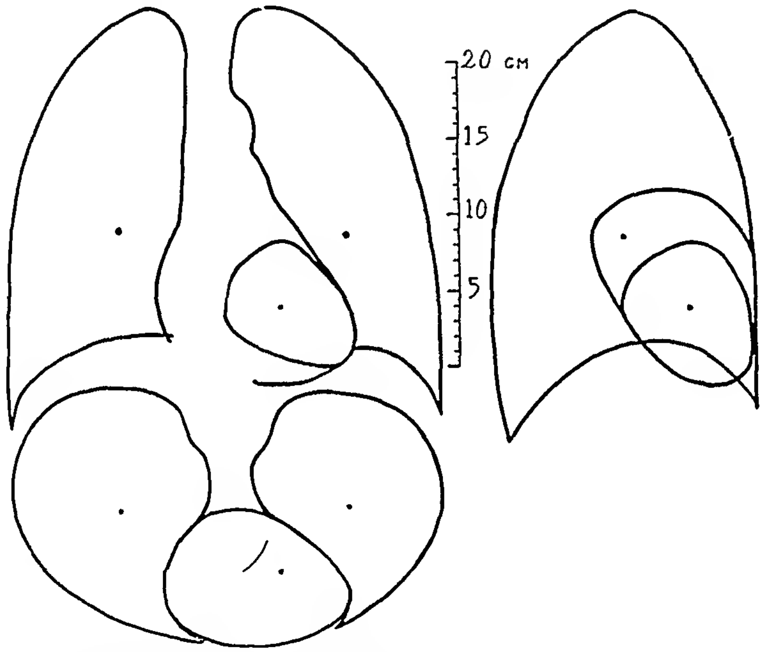

Fig. 1.—The frontal and lateral silhouettes of a normal subject, from roentgen ray films, and the thoracic cross-section drawn from measurements of the films and actual cross-sections.[2] The centers of the lungs and of the left ventricle are indicated by dots; the outlines of the left ventricles and of the mitral aperture are indicated also.

pressure in the left auricle is more altered than in the right, and it is not credible that the slightly engorged right auricle can compress pulmonary veins which have a much higher internal pressure. It seems logical therefore to ascribe the frequent occurrence of right hydrothorax to the fact that pressure in the veins of the right lung must be higher than in the left, since both drain into a common chamber and the right is on the whole more often dependent, and when dependent is much lower than the left. Then, too, the left lung, especially when the heart is enlarged, has less lower lobe surface than the right, and it is the lower lobes which have the highest venous pressure.

That orthopnea cannot be due to high venous pressure in the systemic circuit is apparent in dealing with cases of severe tricuspid valve disease or cases of obstruction to the superior cava. Other evidence against that theory has been presented by Hamilton,[3] by Weiss,[4] and by Calhoun.[5] In patients with ascites or with large pleural exudates orthopnea is occasionally present, and in these cases it must be ascribed not to changes in the lungs primarily, but to the fact that purely thoracic breathing is more effective in the erect position because the fall of the diaphragm lengthens the thoracic compartment available for expansion. When the diaphragm is pressed up by high intraabdominal pressure in the recumbent position or when in the erect position it sags under the weight of several liters of pleural fluid, it is probable that the patient will find it easier to breathe if he sits up. In cardiac patients with hydrothorax, engorged livers, and tympanitic bowels these factors also are operative and may contribute to the preference for the orthopneic posture.

Primarily the patient with heart failure suffers from the high venous pressure behind an inefficient ventricular chamber or a damaged auriculoventricular valve. As the efficiency of the heart's mechanical function fails, venous pressure rises until it reaches a level sufficient to evoke an approximation of the normal minute volume of cardiac output. In the right ventricle of dogs and of men an increase of 1 cm. of water pressure in the veins forces an increase of about 10 per cent in cardiac output, and the study of pulmonary blood flow rate[6] and of vital capacity[7] in hyperthyroidism indicates that the left ventricle responds similarly to slight changes in venous pressure. When the heart fails, a rise of 5, 10, or even 20 cm. of water in venous pressure with a normal or subnormal minute output of blood from the heart indicates how greatly ventricular efficiency has failed—in a normal heart such a rise in venous pressure would cause 50, 80, or 150 per cent rise in minute volume. The degree of impairment in efficiency may be very different in the right and in the left side of the heart, and there often is little change in venous pressure in systemic veins in patients with mitral stenosis or with hypertension, aortic insufficiency, or some other factor which precipitates left ventricular failure and rise in pressure in pulmonary veins. The latter is measured indirectly by the slowing of flow through the dilated lung veins and manifests itself by lowering vital capacity and causing lung engorgement demonstrable in roentgenograms or on auscultation. The general level of pulmonary venous pressure depends then on the level of cardiac output to be maintained, on the level of ventricular efficiency, and on the gravitational gradient between the venous ends of the lung capillaries and the left ventricle. Change of posture is not without influence on the level of cardiac

output, since this may rise 5 to 30 per cent on the assumption of a recumbent position,[8] but there is simultaneously an increase in efficiency of left ventricular systole, due to the fall in diastolic pressure. When the cardiac output in experimental animals[9] is increased without any decrease in peripheral resistance, there is an increase of 10 to 15 per cent in the blood held in the heart chambers and lung vessels due to a 50 per cent increase in cardiac inflow, but one hesitates to accept Hamilton's view that the decrease in vital capacity occurring when normal subjects assume a supine posture is due to the increased cardiac inflow. This only averages a small percentage and is offset by a fall in peripheral resistance and hence a more efficient left ventricular emptying.

When an adult lies down, the blood in his lung capillaries must, as these studies of lung mass and ventricular position indicate, run upward from 3.5 to 7 cm. in order to reach the left ventricle; when he is erect the blood runs downward from 3 to 5.7 cm. before it reaches the ventricle. Since cardiac output depends on the maintenance of an adequate pressure at the venous inlet of the ventricles, and since it is not diminished but may be slightly increased on lying down, the pressure in the ventricle during diastole must be at least as great when the person is recumbent as when he is erect.

To maintain a given level of left ventricular output, the pressure in pulmonary veins will necessarily be from 7.5 to 10 cm. greater in the recumbent than in the erect position. This, of course, refers to the average, but, since in fact most of the lung is distant from the actual center of mass, what actually is meant is that the proportion of the lung in which the venous pressure must be higher than that in the left ventricle is far larger in the recumbent than in the erect posture. Hence, when the venous pressure, elevated as a result of heart failure, is further augmented as a result of lying down, the vital capacity is diminished, pulmonary edema more readily occurs and the Hering-Brener reflexes become more urgent. Respiration becomes shallower and less effective, and dyspnea, which was absent in the sitting posture, becomes progressively more embarrassing. Even in normal individuals there is evidence that the blood content of the lungs is increased on lying down and that all the change in vital capacity is due to this hyperemia.[3] But this is not a shift in blood "stored" in the lower extremities to blood "storage" in the lungs. The blood is merely trapped in the distended veins in dependent parts of the lungs, and, if the general level of the lung veins in relation to the point of outflow into the ventricle were not altered, the lungs would not be affected by change in posture. In theory, cardiac patients should then be less dyspneic when prone than when recumbent, but when prone respiration is effected only by raising the

heaviest parts of the trunk. However, Weiss noted that orthopneic patients when inclined forward had higher vital capacity and less dyspnea than when the angle of the body to the horizontal was the same with the back dependent.[4] This observation can be explained only by the anatomic and hydrostatic relations of heart and lungs.

In all discussions of cardiac dyspnea it must be borne in mind that the subjective sensation is not due merely to overventilation. The cardiac patient is often so uncomfortable that he seeks the relief given by sitting up, when the actual minute volume of ventilation is only one-half or one-third as great as that which causes consciousness of respiratory effort in a normal individual during mild exercise at high altitudes. The respiratory effect of lung hyperemia cannot be explained by the increased minute volume of respiration necessitated by heightened Hering-Brener reflexes and the resulting rapid, shallow, inefficient respiration. Nor is it due to reduced vital capacity, for the tidal air of a dyspneic cardiac patient may be only one-sixth of his vital capacity, while that of an athlete, exercising without respiratory distress, often is one-fourth or one-third the vital capacity. Since the athlete's respiratory rate is also greater than the dyspneic cardiac patient's, it is obvious that the awareness of respiratory effort which makes a recumbent patient sit up is due neither to increase in volume, in rate, nor in percentage of vital capacity used in respiration. The loss of lung elasticity due to hyperemia and the consequent rise in intrathoracic pressure[10, 11] causes the cardiac patient to increase the muscular element in expiration to a much greater degree than occurs in the athlete who is sustaining a tolerable, constant load of physical effort, even though his respiratory rate, minute ventilation, and ratio of $\frac{\text{tidal air}}{\text{vital capacity}}$ are all higher than those of the cardiac patient (Table II). The necessity of using muscular effort in expiration, because of bronchospasm, emphysema with loss of lung elasticity, or experimental narrowing of the chief airway always results in consciousness of respiratory activity, and this is what is meant by dyspnea. The subjective phenomenon which is known as dyspnea, and which often leads to orthopnea in cardiac patients, is due then chiefly (as Wiggers[12] has emphasized) to the need for expiratory effort imposed by loss of lung elasticity. The rise in pulmonary venous pressure of recumbent cardiac patients undoubtedly adds to the stiffness of the lung and diminishes the recoil effect which normally causes expiration. In this way, as much as or more than by reducing vital capacity, it makes the patient aware of the effort of breathing. Observation of overbreathing by patients breathing against the slight but unfamiliar resistance of a spirometer, in tests of basal metabolism, arouses a suspicion that in the cardiac patients who occasionally show low arterial acidity, consciousness of respira-

TABLE II

	MEN WITHOUT DYSPNEA		CARDIAC PATIENTS WITH DYSPNEA IN P.M.		EXERCISING NORMAL AT 70% OF WORK TOLERANCE
	A.M.	P.M.	A.M.	P.M.	
Respiratory rate in minutes	15	16	20	23	23
Total minutes ventilation	6.65 l	7.00 l	8.00 l	9.26 l	42.00
Percentage of normal A.M. minutes ventilation	100%	105%	120%	139%	630%
O_2 intake per minute	250 c.c.	275 c.c.	250 c.c.	275 c.c.	1750 c.c.
R.Q. (from experience with normal and cardiac diets)	0.82	0.86	0.82	0.90	0.95
CO_2 output per minute	205 c.c.	237 c.c.	205 c.c.	247 c.c.	1660 c.c.
Percentage of normal A.M. CO_2 output	100%	115%	100%	120%	810%
Arterial CO_2 tension, mm. Hg	40.5	36.1	45.3	43.3	38.0
Alveolar CO_2 content, per cent	5.3	4.8	6.0	5.7	5.00
Essential ventilation of alveoli per minute	3.66 l	4.71	3.23	4.07	33.2
Ventilation efficiency $\frac{\text{Essential ventilation}}{\text{Total ventilation}}$	55%	67%	41%	44%	79%
Percentage of daily rise in essential ventilation		29%		26%	
Arterial pH	7.435	7.480	7.37	7.39	7.35
Per cent of normal P.M. H ion concentration	111%	100%	129%	123%	135%
Tidal air	443 c.c.	438 c.c.	400 c.c.	403 c.c.	1830 c.c.
Vital capacity	3960 c.c.	3900 c.c.	2400 c.c.	2220 c.c.	4200 c.c.
Diurnal decrease vital capacity		60 c.c.		180 c.c.	
Ratio $\frac{\text{Vital capacity}}{\text{Tidal air}}$	8.9	8.9	6.0	5.5	2.3

NOTE.—From data of Cullen, Harrison, and coworkers (Arch. Int. Med. 53: 724, 1934, and J. B. C. 83: 545, 1929) and for exercise, from L. J. Henderson's data on A.V.B. (who had the same resting arterial blood findings as Cullen's normals) in *Blood,* Yale Press, 1928. At sea level ventilation adequate to wash out CO_2 raises alveolar O_2 tension so high that blood is practically saturated with O_2, and therefore CO_2 output and alveolar tension determine the ventilation requirement. The table shows that normal persons, in spite of a daytime rise in CO_2 output, ventilate their lungs more effectively and lower arterial CO_2 tension and acidity, while cardiac patients with a tendency to dyspnea in spite of bed rest have more acid blood and higher CO_2 tension, effect less reduction in acidity and CO_2 tension by day than normal persons, and have a rise in total ventilation out of proportion to their increased CO_2 output in the evening. All of this points to (1) less efficient pulmonary and nervous mechanism for ventilating the lungs of the cardiac, and (2) less sensitive respiratory center in the cardiac. Comparison with the normal man, exercising vigorously but well below his tolerance for continued effort, shows that the dyspneic cardiac patient breathes no faster, moves only one-fourth as much air each minute, and uses only half as much of the available vital capacity in breathing as does a normal man under conditions in which respiratory distress may not be appreciable. Awareness of respiratory distress in the cardiac patient is apparently not due simply to an elevated rate, or elevated minute volume of respiration, or to decrease in ratio of vital capacity to tidal air.

tory effort causes overventilation and not, as has been suggested, that overventilation is a significant element in causing dyspnea and orthopnea. An examination of the data published by Cullen and his coworkers, as well as those of others who have examined the blood gases of dyspneic cardiac patients, indicates that overventilation is not the rule (using arterial CO_2 tension and pH as indices) but occurs only occasionally (Table II). Diminished sensitivity of the respiratory center is usually found in patients suffering from dyspnea at rest or orthopnea.

Orthopnea, then, is due to the patient's being more aware of and disturbed by his breathing when he lies down than when he sits up. He is aware of his breathing because respiration is labored, that is, because expiration is no longer passive but involves muscular effort, and not simply because he breathes as often or has as high a ratio of tidal volume to vital capacity as normal persons have during the unconscious hyperventilation due to exercise. The breathing is labored because the lungs are relatively inelastic and the normal intrathoracic negative pressure and elastic recoil are decreased. The rise in pulmonic venous pressure necessitated by recumbent posture can contribute to lung inelasticity and raise respiratory effort above the threshold of consciousness.

SUMMARY

When an adult of average size is recumbent, the blood flowing from the pulmonary venous bed must be lifted from 4 to 7 cm. against the force of gravity in order to fill the left ventricle; but when the body is erect, the pulmonary outflow descends from 3 to 5.5 cm. to reach the left ventricle. Thus the pulmonary venous pressure which is adequate in the erect position to maintain a given level of left ventricular filling and cardiac output is lower than that needed to maintain the same level of cardiac output, when the individual is recumbent, by the pressure represented by a column of blood 7.5 to 10 cm. high. In the same way, the pulmonary venous outflow from the right lung of an adult in the right lateral recumbent posture must be lifted 10 cm. or more to reach the left ventricle, that from the left lung, when in the left lateral position, need be lifted only 5 cm. Therefore, the average venous pressure needed to maintain the flow of blood will be much higher in the right lung than in the left, even if the individual spends equal periods lying on the two sides. In patients, like many cardiac patients, who favor the right lateral decubitus, this difference in average pressure between the venous beds in the lungs will be increased. It is suggested that these hydrostatic factors of anatomical origin are of paramount importance in causing orthopnea and the preponderance of right pleural transudation in patients with heart failure.

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FOLLOW-UP STUDY OF SIXTY-FOUR PATIENTS WITH A RIGHT BUNDLE-BRANCH CONDUCTION DEFECT*†

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IN JUNE, 1930, a woman, aged sixty-one years, came in for routine cardiovascular study, "just to be sure everything was all right." Her electrocardiogram showed a bizarre QRS complex (Fig. 1*A*). She had no other evidence of cardiovascular disease: no symptoms, normal blood pressure (105 systolic and 65 diastolic), normal orthodiagram, no murmurs, and no signs of congestive heart failure. She has been studied at intervals since then, the last time on May 10, 1935. Her present cardiovascular status is the same as it was five years ago. The electrocardiogram is unchanged (Fig. 1*B*). She had been known to us for many years prior to 1930 and had never had any cardiac symptoms. We suspect, therefore, that she may have had this deformity of her QRS complex for years before it was found.

When this patient first appeared, we were engaged in studying the electrocardiograms of a group of 1,000 college students and 145 business executives. One student and two business men, with no other evidence of cardiovascular disease, showed this same type of electrocardiogram. Consequently, in 1930, we collected all similar tracings from our files and have periodically followed the cardiovascular status of the patients with them, by means of clinical methods, electrocardiograms, and orthodiagrams. We have added to the group all patients with this type of tracing who have presented themselves since that time‡ and now have a total of sixty-four. The present paper is based upon an analysis of these cases with special reference to their cardiovascular status when first seen and their subsequent clinical course.

I. *Characteristics of the Electrocardiogram.*—The terminal downward deflection of QRS in Lead I and usually its final upward deflection in Lead III are widened, slurred, and notched. The duration of QRS is 0.12 second or more. In the uncomplicated case, the tracing is otherwise normal. Certain variations are seen, which have been classified into four types by Bayley.[1] Wilson[2] and his coworkers have

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‡Dr. William B. Porter, of Richmond, and Dr. James W. Esler, of Washington, have each supplied us with one.

presented evidence that these phenomena in the QRS complex are due to right bundle-branch block. Our observations[3] based upon the time relation of the dynamic events in the two ventricles support this view: right ventricular contraction was delayed in the four patients which were studied. However, histological studies of these cases are not available, and we do not know whether the block of the right bundle branch is complete.

II. *Analysis of the Cardiovascular Findings at the First Examination, of Sixty-Four Cases With a Right Bundle-Branch Conduction Defect.*—Table I tabulates the results. Group A contains twenty patients who when first seen, showed no evidence of heart disease or hypertension, except the QRS deformity. The evidence of peripheral

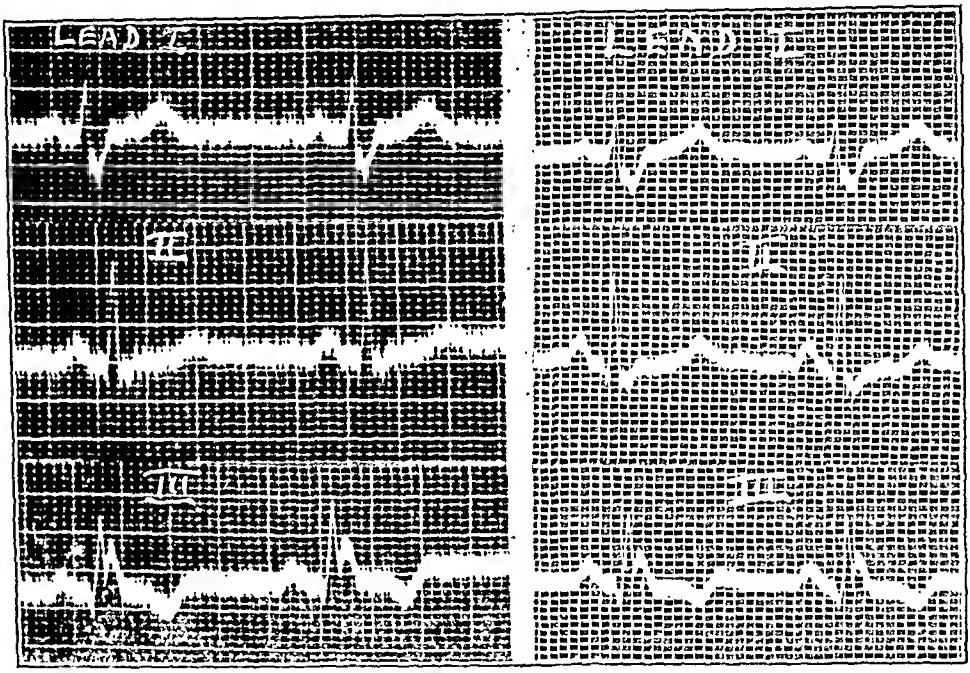

Fig. 1.—*A*, electrocardiogram of a woman, aged sixty-one years, taken on June 23, 1930. She showed no signs or symptoms of cardiovascular disease. The S-wave in Lead I and the R-wave in Lead III are widened and slurred. The QRS interval is 0.13 second. The electrocardiogram is otherwise normal.

B, electrocardiogram of the same patient taken on May 10, 1935, showing no definite change. Her present cardiovascular status is the same as it was five years ago. She has no cardiac symptoms, normal blood pressure, normal orthodiagram, no murmurs, and no signs of congestive heart failure.

vascular sclerosis in all but one of these patients was not out of proportion to age. Nineteen had no peripheral vascular symptoms; one, aged sixty-three years had intermittent claudication. Group B contains fifteen cases which have been classified as having "no very marked evidence of heart disease." Group C contains twenty-nine cases which showed definite evidence of heart disease in addition to the electrocardiographic findings. Fourteen of the sixty-four had other significant electrocardiographic abnormalities besides the QRS

deformity (T-wave inversion, 5 cases; P-R prolongation, 6 cases; auricular fibrillation, 2 cases; paroxysmal ventricular tachycardia, 1 case). If these fourteen cases are removed from the two groups, two from B and twelve from C, fifty remain, of which twenty had no other evidence of heart disease except the QRS deformity. This is a rather striking proportion, especially since all but two of these patients received complete cardiovascular study. Bayley[1] has reported that many patients with bundle-branch block show no physical signs of heart disease. However, these patients did not even have any significant cardiac symptoms.

TABLE I

CLASSIFICATION OF 64 CASES OF RIGHT BUNDLE-BRANCH CONDUCTION DEFECT ON THE BASIS OF THE FIRST EXAMINATION

A. No other evidence of heart disease or hypertension		20
B. No very marked evidence of heart disease		15
Nothing but slight cardiac enlargement	5	
Nothing but vague precordial pain	3	
Nothing but a systolic murmur	1	
Nothing but T-2 inversion	1	
Nothing but P-R prolongation	1	
Hypertension—no enlargement, angina or failure	4	
C. Definite signs of heart disease		29
Etiology not clear	5	
Congenital	2	
Rheumatic	3	
Syphilitic	1	
Hypertension with enlargement, angina or failure	11	
Coronary disease without hypertension	7	

III. *The Age Incidence.*—Table II gives these data. Three-fourths of the patients were over fifty years of age when they were first seen. This fact is of importance with regard to life expectancy. It also suggests that many of the individuals in Group A may have a degenerative lesion in the conduction system, rather than a congenital or an inflammatory one.

TABLE II

AGE OF 64 PATIENTS WITH RIGHT BUNDLE-BRANCH CONDUCTION DEFECT AT TIME OF FIRST EXAMINATION

	0-10 YR.	11-20 YR.	21-30 YR.	31-40 YR.	41-50 YR.	51-60 YR.	61-70 YR.	71-80 YR.
Group A No other evidence of heart disease or hypertension		2	1		2	6	7	2
Group B No very marked evidence of heart disease					1	5	6	3
Group C Definite signs of heart disease	1	1	2	2	4	6	8	5
Total	1	3	3	2	7	17	21	10

IV. *Follow-Up Studies.*—Table III tabulates the follow-up of the cases in the three groups.

TABLE III

FOLLOW-UP OF 64 CASES OF RIGHT BUNDLE-BRANCH CONDUCTION DEFECT

FOLLOW-UP	LOST	LESS THAN 1 YR.	1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	6 YR.	7 YR.	11 YR.	TOTAL
Group A. No evidence of heart disease or hypertension at first examination, except the QRS deformity	1	2		3*	4	4	5	1			20
Group B. No very marked signs of heart disease except the QRS deformity	2	1	1	3†	2	2	2		1	1	15
Group C. Definite signs of heart disease, in addition to the electrocardiographic findings	7	7	3	3	3	3	2		1		29
	10	10	4	9	9	9	9	1	2	1	64

*One case, followed for two years, has not been seen for the last three years.
†One case, followed for two years, has not been seen for the past twelve months.
We have been in contact with all the rest of these patients until the present time, except the ten in the "Lost" column, and eight who have died (see text).

Group A: Four patients in this group have shown a definite change in their status during the follow-up period. One, a man seventy-two years old, developed coronary occlusion and died after having been followed for two years. A second patient, a man aged fifty-seven years, after having been followed for four years, suffered a coronary occlusion in April, 1935, but survived. The other two, males, aged fifty-seven and fifty-nine years, followed for two and five years, respectively, have developed hypertension without enlargement of the heart, congestive failure, or cardiac symptoms. The other patients who have been followed have not developed any new signs or symptoms; they still have no evidence of heart disease, except the QRS deformity.

Group B: Two individuals in this group have shown a definite change in their status during the follow-up period. One man whose only abnormality was a P-R interval of 0.26 second survived a prostatectomy, developed hypertension, and died of apoplexy, at the age of seventy-eight years, after having been followed for three years. The second patient, a sixty-four-year-old woman with hypertension, after being followed for seven years without change, developed hyperthyroidism, congestive failure, and auricular fibrillation. She has

recently had a subtotal thyroidectomy and is recovering. The other cases that have been followed have shown no definite change. One patient, a physician, has been seen at intervals for eleven years since the QRS deformity was first discovered. He has had slight cardiac enlargement and many extrasystoles at each examination. He is now seventy-two years old and is still engaged in active practice.

Thus, in these first two groups of cases, which showed nothing immediately serious in the original findings, except the QRS deformity; twenty-two of thirty-five patients have been followed from two to eleven years without definite change. Three have been lost. Four have developed serious trouble, but in only two of these was the cause of the trouble intrinsically cardiac.

Group C: Six of the twenty-nine patients are known to have died. Four succumbed during the first year of follow-up: one from sarcoma and three from heart disease. Two died during their third year of follow-up: one from carcinoma and one from heart disease. Ten have lived from two to seven years and are still living. These patients fared no worse than one might expect them to on the basis of their cardiovascular lesions, without reference to the QRS deformity.

Of the entire group of sixty-four cases, eight are known to be dead. Ten have been lost. More than half have been followed from two to eleven years and are still alive; more than one-third have been followed for four years or more and are still alive.

DISCUSSION

There are many published reports which deal with the cardiovascular status and prognosis of patients with intraventricular conduction defects.[4] The following are representative excerpts from them: Graybiel and Sprague,[4a] on the basis of a series of 395 cases, state that "bundle-branch block almost invariably indicates serious organic disease of the heart, usually coronary disease; the average duration of life of the 223 fatal cases in this series, after discovery of the conduction fault, was one year and two months, but eighty-five other patients are still alive after an average of two years and eleven months. . . . . . With few exceptions, the patients still living are either seriously limited in their activity or are actually in some stage of cardiac decompensation. Among the fatal cases, the chief cause of death, where this is known, has been, in nearly every instance, cardiac failure. . . . . . Partial bundle-branch block must be regarded clinically as equally significant with complete bundle-branch block, the prognosis in both being essentially the same." King,[4b] on the basis of 150 cases, states: "The prognosis . . . . . is of extreme gravity in bundle-branch block in general." Herrmann and Ashman[4c] write: "Prognostically electrocardiographic findings indicating defective in

traventricular conduction, especially if persistent, are significant of grave myocardial damage." Thus, a review of the literature leaves one with the impression that most cases with an intraventricular conduction defect have serious heart disease, and have, on the average, less than two years to live. It has been recognized that some patients live considerably longer,[5] but it is probably the general feeling that they are exceptional.

Two main facts emerge from our study of this particular group of sixty-four patients with a right bundle-branch conduction defect: (1) *A smaller proportion of them have serious heart disease than the literature on bundle-branch lesions would lead one to expect,* and (2) *the presence of this electrocardiographic abnormality per se, does not seem to add materially to the gravity of prognosis.*

We have found in the literature three references which deal with the clinical status of patients with this type of electrocardiogram. Bayley[1] reviewed seventy cases, together with 103 cases of left bundle-branch block. In speaking of both types together, he states, "The average patient with bundle-branch block shows little evidence of cardiovascular disease on routine physical examination, and one is frequently surprised when the electrocardiogram discloses a serious conduction defect." He does not discuss separately the clinical aspects of his cases of right bundle-branch block, nor compare them with left-sided block. Thus, he leaves unanswered a question which we have likewise failed to answer: How does the cardiovascular status of patients with this right bundle-branch defect compare with that of patients with conduction disturbances of other types? Bayley publishes no follow-up studies. He does not state that any of his cases have no evidence of heart disease except the electrocardiographic abnormality. Von Deesten and Dolganos[6] in a paper entitled "Atypical Bundle-Branch Block With a Favorable Prognosis" report five patients with the QRS deformity which is the subject of our paper. None of their cases presented evidence of serious heart disease, and four of them were followed for eleven, eight, four, and three years, respectively, without much change. Oppenheimer, in a recent personal communication, stated that a study by himself, Rothschild and Mann,[7] which appeared in abstract in 1925 also dealt with this type of case. Nine of their ten patients showed no downward progress during the period of follow-up. The reports of von Deesten and Dolganos and of Oppenheimer, Rothschild, and Mann are the only papers we have found which view an intraventricular conduction defect with optimism. Their observations leave one with the impression, however, that the cardiovascular status of these patients is better than a larger series of cases shows it to be.

Several other points seem worth emphasizing:

1. Of the fourteen patients with other significant electrocardiographic abnormalities, in addition to the QRS deformity (such as T-wave inversion, P-R prolongation, auricular fibrillation, and paroxysmal ventricular tachycardia) twelve had definite evidence of cardiovascular disease at the first examination in addition to the electrocardiographic phenomena. Only two patients did not, and one of them developed hypertension and died. It seems, therefore, that T-wave inversion, and the other abnormalities referred to, have their usual significance when they appear in these cases. Three of the sixty-four patients had a significant Q-wave[8] in Lead III; one case in Group B and two in Group C. Many other patients just escaped having a significant Q_3 by virtue of a small upward deflection preceding the downward deflection of QRS.

2. Chest leads were taken in twenty cases. Bizarre curves were obtained. In some instances, especially with the anterior electrode in the third left interspace near the sternum (Fig. 2*A*), the tracings bore a superficial resemblance to those obtained in acute coronary occlusion. It should be emphasized that bundle-branch block (a) may appear during an attack of acute coronary occlusion and mask the electrocardiographic signs of this lesion[9] or (b) may produce RS-T interval deviations in the absence of recent cardiac infarction which may be mistakenly interpreted as evidence of coronary occlusion.

3. We have seen this QRS deformity make its appearance in three patients while they were under our observation.[10] The first was a forty-nine-year-old man, who had no evidence of cardiovascular disease when first seen in 1930. In 1930, 1931, and 1932 his tracing was normal. In 1933, 1934, and 1935 it showed the QRS deformity. There were no symptoms of onset that we could elicit. The cardiac shadow has been slightly enlarged throughout. He is classified in Group B. The second case was that of a man, aged sixty-nine years, with anginal pain and definite coronary artery disease. In 1932 and 1933 the QRS complex was normal. In 1934 the QRS deformity appeared and persisted until his death from carcinoma of the head of the pancreas. There were no clear-cut symptoms accompanying the appearance of the QRS deformity. He is classified in Group C. The third patient was a man fifty years old who developed this QRS deformity during a fatal attack of acute coronary occlusion.[9a]

4. There were three cases in which the QRS deformity appeared and disappeared from time to time[4c, 11] (Fig. 2*B*).

5. These cases of right bundle-branch defect differ in several respects from the cases with short P-R interval, QRS deformity and good prognosis reported by Wolff, Parkinson and White,[12] which may be due to a functioning bundle of Kent:[13] (a) The P-R interval is

not short. (b) In the three patients mentioned above, in whom the QRS deformity appeared and disappeared, the P-R interval and the initial deflection of QRS did not change (Fig. 2*B*). (c) The widening and slurring involve the terminal portion of QRS, not its initial deflection. (d) In one patient who had a paroxysm of tachycardia, the QRS complex deformity was present before, during, and after the paroxysm. In the cases reported by Wolff and his associates, it tended to disappear during paroxysmal arrhythmia.

6. The physical signs of this lesion are not diagnostic. Many patients have split heart sounds. However, the frequency of this finding in the absence of QRS prolongation makes it an unreliable diagnostic sign.[3]

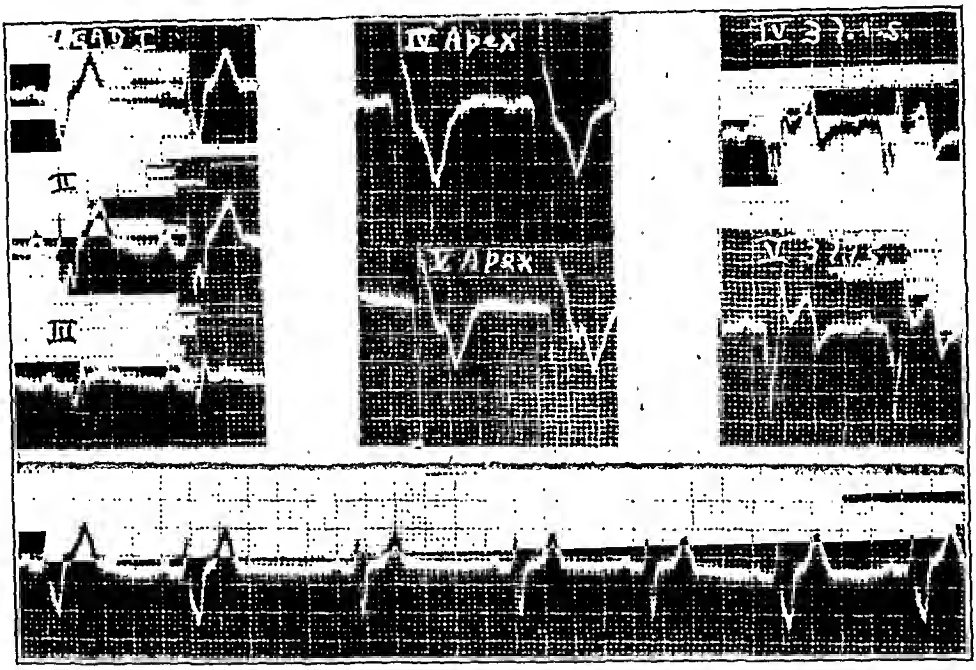

Fig. 2.—Electrocardiograms of a boy aged nineteen years, with a right bundle-branch defect, a rough systolic murmur and thrill at the fourth left interspace near the sternum, slight enlargement of the heart, blood pressure of 110/60, fairly good exercise tolerance, and no signs of active cardiac disease. He probably has a congenital interventricular septal defect.

A, shows the limb leads and the chest leads numbered as in previous publications.[14] At the extreme right are Leads IV and V, taken with the anterior chest electrode in the third left interspace, near the sternum. These tracings present an appearance which might be mistakenly interpreted as evidence of recent cardiac infarction.

B, shows Lead I in the same case. The QRS deformity disappeared for three beats. The P-R interval and the initial deflection of QRS did not change.

7. Bayley[1] has classified his cases of right bundle-branch block into four groups. Our cases can be similarly classified: Type I, 23 cases; Type II, 6 cases; Type III, 32 cases; Type IV, 3 cases. However, correlations between this grouping and other factors, such as age, sex, heart size, or degree of cardiac damage, are not striking.

8. There are forty-six males and eighteen females in the group.

9. The frequency of this electrocardiographic abnormality in the general population is not known. Bayley's observations suggest that the term "rare" type of bundle-branch block is a misnomer. Our cardiovascular survey of 1,300 unselected college students* and 145 unselected business executives over forty-five years of age has some bearing upon this point. None of the 1,300 college students had left bundle-branch block; two of the 1,300 showed this right bundle-branch defect. One is classified in Group A and one in Group C. Among the 145 business executives over forty-five years of age, none had left bundle-branch block; five showed this right bundle-branch defect. Two of these are classified in Group A, two in Group B, and one in Group C. Although three of these five had other evidences of heart disease when first seen (one case, T_2 inversion; the second, slight cardiac enlargement; the third, moderate cardiac enlargement), none of them had cardiac symptoms. All have been followed for five years without any striking change. On the basis of these observations it would seem likely that there are a considerable number of people over forty-five years of age with this QRS deformity, who are blissfully unaware of its existence. Most of them will lead a life of average comfort and happiness unless someone discovers it and makes them give up part of their pleasure and freedom. Since we have not restricted the activity of any patients in this group on strictly electrocardiographic grounds, their longevity cannot be ascribed to a life of rigorous self-denial.

SUMMARY

1. Sixty-four patients with electrocardiograms of the type shown have been studied carefully and many of them followed over a period of years.

3. If fourteen cases with other significant electrocardiographic abnormalities are excluded, fifty cases remain. Of these, twenty showed no evidence of heart disease when first seen, except the QRS deformity, thirteen showed relatively minor evidences of heart disease, and seventeen showed definite evidence of heart disease.

3. Follow-up: The patients with little or no other evidence of heart disease did well on the whole, when one considers that three-fourths of them were over fifty years old when first seen. Those with definite evidence of heart disease seemed to follow the clinical course expected of their lesions without reference to the abnormality of the QRS complex.

4. When this type of electrocardiogram is found in a patient with no other evidence of heart disease, it is not necessarily an ominous

*One thousand students were studied in 1929 and an additional 300 in 1934.

prognostic sign. Its presence per se in a group of patients does not seem to add materially to the gravity of their prognosis.

5. These facts seem worthy of emphasis since most patients with intraventricular conduction defects have been regarded as having serious heart disease and a grave prognosis.

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THE RELATIONSHIP OF HEART-BLOCK, AURICULOVENTRICULAR AND INTRAVENTRICULAR, TO CLINICAL MANIFESTATIONS OF CORONARY DISEASE, ANGINA PECTORIS, AND CORONARY THROMBOSIS

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INTRODUCTION

FOR many years investigators have studied the functional and structural pathological conditions that disturb the conduction system of the heart to cause heart-block. The use of electrocardiography has resulted in a great advance in the detection of heart-block of various kinds and grades. On the other hand, our understanding about certain anatomicopathological lesions of the conduction system has remained obscure; there is a discrepancy between the two sets of data in the present state of our knowledge, a gap which will eventually be lessened or abolished after a more extensive study of the correlation of the clinical manifestations of heart-block with structural lesions and functional defects in the conduction system.

While awaiting the time when we shall have a complete understanding of the relationship between heart-block (of various types and grades) and pathological changes in the conduction system of the heart or in the blood vessels supplying it, we should make use of any clues that we have already at hand in assessing the relationship between heart-block and coronary disease. Such clues we possess in the determinations of the incidence of the known clinical manifestations of coronary disease, namely, paroxysmal angina pectoris and coronary thrombosis, in cases with heart-block, and, conversely, of the incidence of heart-block of various types in cases with paroxysmal angina pectoris or coronary thrombosis. In the present study we have made such analyses; that is, of the relationships between the clinical manifestations of coronary disease and the various types of heart-block.

A delay in auriculoventricular conduction time exceeding 0.20 of a second for the P-R interval of the electrocardiogram is considered, in this study, as indicative of auriculoventricular block. We have

divided intraventricular block into three groups, in accordance with the electrocardiographic variations (and not necessarily in accordance with structural lesions of the conduction system). Lesser degrees of intraventricular block are considered present when there exists a widening of the QRS complexes which exceeds 0.11 second, with slurring and notching but without the characteristics of full bundle-branch block. Full left bundle-branch block is considered present in those cases in which, with the duration of the ventricular complexes more than 0.11 second, there is left axis deviation. Full right bundle-branch block shows wide QRS waves with right axis deviation. In accordance with the latest studies of Wilson and his coworkers on bundle-branch block we have included under right bundle-branch block cases whose electrocardiograms show very wide S-waves in Lead I and under left bundle-branch block cases whose electrocardiograms show wide upright QRS waves in all leads; the former are common, the latter rare, a fact that tends somewhat to equalize the numbers of right and of left bundle-branch block. It was once believed that there existed a very great preponderance of left bundle-branch block.

In the present analysis we have not included the rare cases of apparent bundle-branch block (wide QRS waves) with short P-R intervals, since these cases are to be classified, not as intraventricular block, but rather as very early spreading of the impulse to one ventricle or the other.[1, 2]

LITERATURE

Here and there in the literature there have been brief observations as to the presence of heart-block in coronary disease and as to the presence of clinical evidences of coronary disease in heart-block, but the correlation of the two relationships has not, so far as we have discovered, been the subject of special study such as we have made and are reporting here. The practical importance of the study is evident, as well as is its academic interest.

A few references to large series of cases of angina pectoris and coronary thrombosis and of heart-block that have been published are as follows:

Levine[3] in 1929 noted disorders of heart rhythm in cases of coronary thrombosis, especially those that concern premature beats and the sudden development of heart-block, which may be related to the localization of the infarct. He said that in general the appearance of heart-block during coronary thrombosis is an unfavorable sign, though he believed that a slight delay in conduction was not important. He reported that the immediate mortality in his series of 143 cases of coronary thrombosis was 53 per cent and that the average duration of life was twenty-four months in the patients who survived the im-

mediate illness; the average age was 54.7 years; he did not give data concerning the relative prognosis of coronary thrombosis with auriculoventricular and with intraventricular block.

Conner and Holt[4] analyzed 287 patients with coronary thrombosis. Approximately 85 per cent of these cases occurred in men and 15 per cent in women. One hundred and fifty-one of these patients had one or more electrocardiograms taken. Those individuals who did not show heart-block did better than those with heart-block. The authors found a mortality of 16.2 per cent in the whole group at the time of the first attack. They said in particular that patients with evidence of arborization or bundle-branch block did poorly.

White and Bland[5] in their study of the prognosis of 500 cases of angina pectoris and of 200 cases of coronary thrombosis, found an average duration of life of 4.4 years after the onset of the disease in 213 fatal cases of angina pectoris, and 1.5 years after the onset in 101 fatal cases of coronary thrombosis. They said, "The electrocardiogram was of little help in predicting the outcome, although a 'coronary' type of T-wave in Lead I or II was seen more often in the patients who died early. . . . The electrocardiogram did not help appreciably in this series." This last statement concerned the prognosis of coronary thrombosis.

Graybiel and Sprague,[6] who made an analysis of 395 cases of bundle-branch block, concluded:

"From the standpoint of diagnosis and prognosis it is important to determine its presence in cardiac patients.

"Bundle-branch block almost invariably indicates serious organic disease of the heart, usually coronary disease; the average duration of life of the 223 fatal cases in this series after the discovery of the conduction fault was one year and two months, but 85 other cases are still alive after an average of two years and eleven months following the discovery of the bundle-branch block.

"Partial bundle-branch block must be regarded clinically as equally significant with complete bundle-branch block, the prognosis in both being essentially the same."

Graybiel and White[7] in a study of 72 cases of complete auriculoventricular block, not yet published, have found that the average age at the time of discovery of the block was fifty-three years, the average duration of life after this discovery in 41 cases that died of heart disease was two years and two months and in 8 patients who died of other causes was six years and eight months and that the average duration of life to date in 17 living patients is six years and eleven months, a more favorable prognosis therefore than in the cases of bundle-branch block reported by Graybiel and Sprague.* Among the

*Six of the 72 patients of the series of Graybiel and White have not yet been heard from in the follow-up study.

72 cases of complete heart-block, 9 had angina pectoris without clinical coronary thrombosis, 4 had coronary thrombosis without angina pectoris, and 3 had both.

PRESENT STUDY

THE INCIDENCE OF HEART-BLOCK AMONG PATIENTS SHOWING CLINICAL EVIDENCE OF CORONARY DISEASE

Among 4,274 cases with signs or symptoms of cardiovascular disease in which electrocardiograms were made and which make up the total number of cases analyzed in the present study, 1,028, or 24 per cent, showed clinical evidence of coronary disease, namely, paroxysmal angina pectoris or coronary thrombosis, or both, in the following proportion: paroxysmal angina pectoris alone, 700 cases or 68+ per cent; coronary thrombosis alone, 169 cases or 16+ per cent; paroxysmal angina pectoris and coronary thrombosis, 159 cases or 15+ per cent.

TABLE I

TOTAL CASES OF CORONARY DISEASE DIAGNOSED CLINICALLY AND BY ELECTROCARDIOGRAPH (PAROXYSMAL ANGINA PECTORIS OR CORONARY THROMBOSIS)

Paroxysmal angina pectoris alone			700		
Coronary thrombosis alone			169		
Paroxysmal angina pectoris and coronary thrombosis			159		
				1,028	
Auriculoventricular or intraventricular block			105		
Both auriculoventricular and intraventricular block			5	110	10.7+%
Auriculoventricular block, total cases				25	2.4+%
Complete	5	0.4+%			
Partial	16	1.6–%			
Transient (partial)	4	0.4–%			
Intraventricular block, total cases				85	8.2+%
Lesser degrees	35	3.4+%			
Left bundle-branch block	40	3.9–%			
Right bundle-branch block	10	0.9–%			

Total cases of coronary disease diagnosed clinically equaled 24% of total of series of cardiovascular cases electrocardiographed (4,274)

A. *Group With Angina Pectoris.*

TABLE II

PAROXYSMAL ANGINA PECTORIS WITHOUT CORONARY THROMBOSIS (CLINICAL DIAGNOSIS)			700	
Auriculoventricular or intraventricular block			62	8.8 %
Both			3	0.4 %
Auriculoventricular block, total cases			11	1.5 %
Complete	1	0.1+%		
Partial	9	1.2+%		
Transient (partial)	1	0.1+%		
Intraventricular block, total cases			54	7.7 %
Lesser degrees	21	3.0 %		
Left bundle-branch block	27	3.8+%		
Right bundle-branch block	6	0.8+%		

TABLE III

PAROXYSMAL ANGINA PECTORIS, ALL CASES			859	
Auriculoventricular or intraventricular block			78	9.1–%
Both			3	0.3+%
Auriculoventricular block, total cases			13	1.5+%
Complete	2	0.2+%		
Partial	10	1.1+%		
Transient (partial)	1	0.1+%		
Intraventricular block, total cases			68	7.9 %
Lesser degrees	26	3.0+%		
Left bundle-branch block	35	4.0+%		
Right bundle-branch block	7	0.8+%		

B. *Group With Coronary Thrombosis.*

TABLE IV

CORONARY THROMBOSIS (CLINICAL DIAGNOSIS), ALL CASES			328	
Auriculoventricular block or intraventricular block			43	13.1+%
Both			2	0.6+%
Auriculoventricular block, total cases			14	4.2+%
Complete	4	1.2+%		
Partial	8	2.4+%		
Transient (partial)	2	0.6+%		
Intraventricular block, total cases			31	9.5 %
Lesser degrees	12	3.7–%		
Left bundle-branch block	14	4.3–%		
Right bundle-branch block	5	1.5+%		

TABLE V

CORONARY THROMBOSIS (CLINICAL DIAGNOSIS) WITHOUT PAROXYSMAL ANGINA PECTORIS			169	
Auriculoventricular or intraventricular block			27	15.9+%
Both			2	1.1+%
Auriculoventricular block, total cases			12	7.1–%
Complete	3	1.7+%		
Partial	7	4.1+%		
Transient (partial)	2	1.2 %		
Intraventricular block, total cases			17	10.0 %
Lesser degrees	7	4.1+%		
Left bundle-branch block	6	3.5+%		
Right bundle-branch block	4	2.3+%		

THE INCIDENCE OF CLINICAL EVIDENCE OF CORONARY DISEASE AMONG CASES SHOWING HEART-BLOCK

We shall now analyze the cases of heart-block found in the total group of patients with cardiovascular symptoms or signs (4,274) of whom electrocardiograms were made with respect to clinical manifestations of coronary disease.

TABLE VI

TOTAL CASES OF HEART-BLOCK	274	
Auriculoventricular block, total cases	117	
Intraventricular block, total cases	181	
Auriculoventricular and intraventricular block, total cases	24	
Coronary disease evident clinically	110	40+%
Paroxysmal angina pectoris alone	65	23.7 %
Paroxysmal angina pectoris, total cases	81	29.5+%
Coronary thrombosis, total cases	45	16.4+%
Coronary thrombosis alone	29	10.5+%
Paroxysmal angina pectoris and coronary thrombosis	16	5.8 %

Total cases of heart-block equaled 6.4 per cent of the total of series of cardiovascular cases electrocardiographed (4,274).

Among the 24, or 20.5+ per cent, of the 117 patients with auriculoventricular block who showed at the same time intraventricular block, only 5 belonged to the group in which the block was related to clinical evidence of coronary disease. The proportion was as follows: 2 patients with partial auriculoventricular block combined with intraventricular block (lesser degrees) had paroxysmal angina pectoris alone; 1 patient with partial auriculoventricular block combined with intraventricular block (lesser degree) had coronary thrombosis alone; 1 patient with partial auriculoventricular block combined with intraventricular block (left bundle-branch block) had paroxysmal angina pectoris alone; and, finally, the fifth patient, showing complete auriculoventricular block combined with intraventricular block (right bundle-branch block), had coronary thrombosis alone.

A. *Group With Auriculoventricular Block.*

TABLE VII

	COMPLETE	PARTIAL	TRANSIENT COMPLETE	TRANSIENT PARTIAL	TOTAL	
Total cases of auriculoventricular block	22	86	2	7	117	
Clinical evidence of coronary disease, total cases	5	16	0	4	25	21.3+%
Paroxysmal angina pectoris alone	1	9	0	1	11	9.4+%
Paroxysmal angina pectoris total	2	10	0	1	13	11.1+%
Coronary thrombosis total	4	8	0	2	14	11.9+%
Coronary thrombosis alone	3	7	0	2	12	10.2+%
Paroxysmal angina pectoris and coronary thrombosis	1	1	0	0	2	1.7+%
Intraventricular block, total cases					24	20.5+%

Total cases of auriculoventricular block equaled 2.4 per cent of total of series of cardiovascular cases electrocardiographed (4,274).

B. *Group With Intraventricular Block of All Degrees.*

TABLE VIII

TOTAL CASES OF INTRAVENTRICULAR BLOCK			181	
Lesser degrees	85			
Left bundle-branch block	77			
Right bundle-branch block	19			
Clinical evidence of coronary disease, total cases			85	46.9+%
Paroxysmal angina pectoris alone	54	29.8+%		
Paroxysmal angina pectoris total	68	37.5+%		
Coronary thrombosis total	31	17.1+%		
Coronary thrombosis alone	17	9.3+%		
Paroxysmal angina pectoris and coronary thrombosis	14	7.7+%		
Auriculoventricular block			24	13.3+%
Complete	4	2.2+%		
Partial	20	11.0+%		
Transient	0			

Total cases of intraventricular block equaled 4.2 per cent of total of series of cardiovascular cases electrocardiographed (4,274).

C. *Left Bundle-Branch Block.*

TABLE IX

TOTAL CASES OF LEFT BUNDLE-BRANCH BLOCK			77	
Coronary disease evident clinically, total cases			41	53.2 %
Paroxysmal angina pectoris alone	27	35.0+%		
Paroxysmal angina pectoris total	35	45.4+%		
Coronary thrombosis total	14	18.1+%		
Coronary thrombosis alone	6	7.7+%		
Paroxysmal angina pectoris and coronary thrombosis	8	10.3+%		
Auriculoventricular block			4	5.1+%
Complete	1	1.2+%		
Partial	3	3.8+%		
Transient	0			

Total cases of left bundle-branch block equaled 1.8 per cent of total of series of cardiovascular cases electrocardiographed (4,274).

D. *Right Bundle-Branch Block.*

TABLE X

TOTAL CASES OF RIGHT BUNDLE-BRANCH BLOCK			19	
Coronary disease evident clinically, total cases			11	57.8+%
Paroxysmal angina pectoris alone	6	31.5+%		
Paroxysmal angina pectoris total	7	36.7+%		
Coronary thrombosis total	5	26.3+%		
Coronary thrombosis alone	4	21.0+%		
Paroxysmal angina pectoris and coronary thrombosis	1	5.2+%		
Auriculoventricular block			2	10.5 %
Complete	1	5.2+%		
Partial	1	5.2+%		
Transient	0			

Total of cases of right bundle-branch block equaled 0.4 per cent of total of series of cardiovascular cases electrocardiographed (4,274).

We would interpolate at this point, with especial regard to prognosis, data concerning a number of the patients with auriculoventricular heart-block, whose etiological factors, so far as clinical evidence goes, are other than coronary disease.

TABLE XI

ETIOLOGICAL FACTORS OTHER THAN EVIDENT OR PROBABLE CORONARY DISEASE RESPONSIBLE FOR AURICULOVENTRICULAR BLOCK

TOTAL CASES OF AURICULOVENTRICULAR BLOCK	117	
Acute or subacute rheumatic infection (among 63 cases)	6	5.1 %
Cardiovascular syphilis (among 81 cases; 1 other case had intraventricular block)	1	0.08%
Congenital heart-block	3	2.5 %
Digitalis intoxication (among 41 cases)	9	8.5 %
Diphtheria (among 4 cases)	2	1.6 %
Leaving a balance of cases of coronary disease or of unknown etiology	96	

Among the 4,274 cases in which electrocardiograms were made, there were, as noted in the table, 41 cases with manifestations of digitalis intoxication but only 9 of these showed auriculoventricular block. We can feel reasonably certain that digitalis given to a few of the patients with coronary thrombosis was not responsible for the infrequent heart-block among such patients. Among these same 4,274 patients, 81 had cardiovascular syphilis, and only 1 of these showed auriculoventricular block; 63 had acute or subacute rheumatic infection, and only 6 of these showed auriculoventricular block; 4 had diphtheria, and 2 of these showed auriculoventricular block, and finally, 3 cases showed congenital heart-block. Only one of the 81 cases of syphilis showed intraventricular block. Digitalis was apparently not responsible for intraventricular block in any of our cases, nor was rheumatic infection. The group with diphtheria was too small to be of any significance.

THE PROGNOSIS OF THE CASES OF HEART-BLOCK ACCORDING TO THE PRESENCE OR ABSENCE OF CLINICAL EVIDENCE OF CORONARY DISEASE

With relation to the prognosis in the patients who have shown heart-block, we have made a division into two groups, namely, those with and those without clinical evidence of coronary disease; it is necessary to subdivide them further as follows: (a) patients alive at last report in whom we cannot foretell the probable duration of life; and (b) patients who are known to have died. In nearly every instance in this latter group death was due to the heart disease.

A. *Prognosis of Cases of Auriculoventricular Block.*—Of the 25 patients with auriculoventricular block with angina pectoris or coronary thrombosis or both, nine were alive at last report. Our records show duration of life according to age after the discovery of heart-

block until the last report as follows: four patients, between 50 and 60 years of age have lived 8, 3, 0.8, and 0.03 years, respectively; three patients, between 60 and 70 years of age, have lived 4, 2, and 0.75 years, respectively; and two patients over 70 years old have lived 3, and 0.08 years, respectively.

The remaining 16 of the 25 patients with auriculoventricular block with angina pectoris or coronary thrombosis or both have died.* Their duration of life according to age after the discovery of heart-block was as follows: five patients under 50 years of age lived 10, 2, 1, 1, and 0.16 years, respectively; five between 50 and 60 years of age lived 2, 1, 0.66, 0.16, and 0.03 years, respectively; four patients between 60 and 70 years of age lived 1, 0.25, 0.16, and 0.003 years, respectively; and two patients over 70 years old lived 9 and 1 years, respectively.

Of the 92 patients with auriculoventricular block without either paroxysmal angina pectoris or coronary thrombosis, 26 of those followed up were alive at the last report. Our records show the duration of life according to age after the discovery of heart-block until last report, as follows: seven patients under 50 years of age have lived 10, 5, 1, 0.75, 0.66, 0.5, and 0.4 years, respectively; six patients between 50 and 60 years of age have lived 17, 6, 1, 1, 0.16, and 0.03 years, respectively; ten patients between 60 and 70 years old have lived 11, 8, 3, 2, 2, 2, 2, 1, 0.33, 0.08 years, respectively; and three patients over 70 years old have lived 3, 0.16, and 0.08 years, respectively. To the group of living patients belong sixteen additional patients not followed up and fifteen patients with auriculoventricular block due to digitalis intoxication or other factors previously mentioned.

The remaining 35 of the 92 patients with auriculoventricular block without angina pectoris or coronary thrombosis have died.† Their duration of life according to age after the discovery of block was as follows: four patients under 50 years of age lived 2, 0.83, 0.25, and 0.08 years, respectively; four patients between 50 and 60 years old lived 6, 3, 1, and 1 years, respectively; seven patients between 60 and 70 years old lived 2, 2, 2, 1, 0.25, 0.047, and 0.021 years, respectively; and sixteen patients over 70 years old lived 4, 2, 1, 1, 0.9, 0.83, 0.75, 0.41, 0.33, 0.25, 0.16, 0.16, 0.08, 0.02, 0.02, 0.003 years, respectively. To the above must be added four patients who showed auriculoventricular block due to various other factors previously mentioned, and which cases we have not taken into present account so far as prognosis is concerned.

*Six of these patients died suddenly (two in recognized attacks of angina pectoris); eight died of congestive failure (one in acute pulmonary edema); and two died apparently in Adams-Stokes attacks.

†Seven of these patients died suddenly; eight died of congestive failure (one in acute pulmonary edema); four died in Adams-Stokes attacks, ten with noncardiac lesions, and six of unknown causes.

Summarizing the above described groups, we find the average age at, and average duration of life after, the discovery of auriculoventricular block as follows:

Patients (25) who have shown auriculoventricular block with paroxysmal angina pectoris or coronary thrombosis or both: nine were alive at the last report, average duration of life, after discovery of block 29.3 months, average age 61.4 years; sixteen died, average duration of life after discovery of block 22.4 months, average age 55.2 years. Patients (57) who have shown auriculoventricular block without either paroxysmal angina pectoris or coronary thrombosis and without other known etiological factors: twenty-six were alive at the last report, average duration of life after discovery of block 41.2 months, average age 48.8 years; thirty-one have died, average duration of life after discovery of block 13 months, average age 60 years.

B. *Prognosis of Cases of Intraventricular Block.*—Of the 85 patients with intraventricular block with paroxysmal angina pectoris or coronary thrombosis or both, 31 were alive at last report. Our records show the duration of life according to age after discovery of the block until last report in the cases followed up as follows: two patients under 50 years old have lived 8 and 3 years, respectively; nine patients between 50 and 60 years of age have lived 8, 5, 3, 3, 1, 1, 0.5, 0.4, and 0.01 years, respectively; eight patients between 60 and 70 years old have lived 3, 3, 2, 1, 1, 1, 0.66, and 0.33 years, respectively; and four patients over 70 years old have lived 5, 1, 0.5, and 0.02 years, respectively. Eight patients were not followed up.

Fifty-four of the 85 patients with intraventricular block with angina pectoris or coronary thrombosis are known to have died.* Their duration of life according to age after the discovery of the block was as follows: two patients under 50 years of age lived 2 and 0.16 years, respectively; twenty-two patients between 50 and 60 years old lived 5, 5, 3, 2, 2, 1, 1, 1, 1, 1, 1, 1, 0.83, 0.75, 0.5, 0.41, 0.41, 0.33, 0.25, 0.16, 0.08, and 0.003 years, respectively; twenty-two patients between 60 and 70 years old lived 11, 8, 6, 5, 4, 3, 3, 2, 2, 1, 0.66, 0.58, 0.41, 0.33, 0.33, 0.33, 0.33, 0.26, 0.25, 0.25, 0.07, and 0.02 years, respectively; and eight patients over 70 years old lived 1, 1, 1, 0.66, 0.5, 0.33, 0.25, and 0.08 years, respectively.

Of the 96 patients of intraventricular block without paroxysmal angina pectoris or coronary thrombosis and without other known etiological factors 54, including 16 patients not followed up, belong to the group alive at the last report, and our records show duration of life according to age after the discovery of block until last report as follows: four patients under fifty years of age have lived 5, 0.75,

*Thirty-seven of these patients died suddenly (several in recognized attacks of angina pectoris), and twelve others are known to have died with congestive failure (two in acute pulmonary edema).

0.58, and 0.16 years, respectively; nine patients between 50 and 60 years old have lived 8, 5, 3, 3, 0.5, 0.5, 0.33, 0.05, and 0.03 years, respectively; fifteen patients between 60 and 70 years old have lived 11, 9, 5, 4, 3, 3, 2, 2, 2, 2, 1, 0.5, 0.5, 0.08, and 0.05 years, respectively; and ten patients over 70 years old have lived 6, 5, 3, 3, 3, 1, 0.16, 0.08, 0.06, and 0.04 years, respectively. The other 42 patients are known to have died;* their duration of life according to age after the discovery of block was as follows: five patients under 50 years of age lived 3, 2, 2, 0.66, and 0.25 years, respectively; thirteen patients between 50 and 60 years old lived 9, 5, 3, 2, 1, 1, 1, 0.66, 0.5, 0.33, 0.16, 0.08, and 0.05 years, respectively; eleven patients between 60 and 70 years old lived 3, 2, 2, 2, 2, 1, 1, 1, 1, 0.41, and 0.16 years, respectively; and thirteen patients over 70 years old lived 6, 3, 2, 1, 1, 1, 0.83, 0.75, 0.66, 0.33, 0.25, 0.16, and 0.06 years, respectively.

Summarizing the data on the above described groups of intraventricular block, we find an average duration of life as follows:

Of patients (85) who have shown intraventricular block with paroxysmal angina pectoris or coronary thrombosis or both: 23 patients followed up were alive at the last report, average duration of life after the discovery of block 27 months, average age 61 years; 54 patients died, average duration of life after discovery of the block 18 months, average age 60.7 years; the remaining 8 patients were not followed up. Of patients (96) who have shown intraventricular block without paroxysmal angina pectoris or coronary thrombosis and without other known etiological factors: 54 patients were alive at the last report, average duration of life after discovery of block 29 months, average age, 62 years; 42 patients died, average duration of life after discovery of block 18.8 months, average age† 61.1 years.

SUMMARY AND CONCLUSIONS

Our attention has been drawn during the past year to the fact that, contrary to one's first expectation and to general impressions, there is a marked discrepancy between the occurrence of auriculoventricular and intraventricular block and the clinical evidence of coronary disease, namely, angina pectoris and gross myocardial infarction. Therefore, we have determined the relative incidence of concurrence of auriculoventricular and intraventricular block, as shown by electrocardiography, and of angina pectoris and of coronary thrombosis in a large series of patients with cardiovascular symptoms or signs carefully studied by ourselves during the past fifteen years.

*Ten of these patients are known to have died suddenly; fifteen died in congestive failure (one in an attack of cardiac asthma), one died during an attack of coronary thrombosis, and one in an Adams-Stokes attack.

†The average age is based on the cases with known ages, and not on the total number of cases, as there are missing records in a few instances.

We have found that only 8.8 per cent of 700 patients with angina pectoris uncomplicated by clinical coronary thrombosis showed heart-block, either auriculoventricular block (1.1 per cent) or intraventricular block (7.3 per cent), or both (0.4 per cent), and that only 13.1 per cent of 328 cases of coronary thrombosis, with or without angina pectoris, showed heart-block, either auriculoventricular block (3.6 per cent) or intraventricular block (8.9 per cent) or both (0.6 per cent).

Conversely, of 117 patients with auriculoventricular block in the series, only 9.4 per cent had angina pectoris without clinical coronary thrombosis, and only 11.9 per cent more had clinical evidence of coronary thrombosis with or without angina pectoris, making a grand total of 21.3 per cent of cases of auriculoventricular block with clear evidence of coronary disease.

Finally, of 181 cases of intraventricular block of all grades, including 77 cases of full left bundle-branch block and 19 cases of full right bundle-branch block, 29.8 per cent showed angina pectoris without clinical coronary thrombosis, and only 9.3 per cent showed coronary thrombosis with or without angina pectoris, making a grand total of 46.9 per cent of cases of intraventricular block with clear evidence of coronary disease. Details as to the relationship of left and right bundle-branch block to clinical manifestations of coronary disease have been presented; in both groups a few over half had angina pectoris, coronary thrombosis, or both.

It is evident that coronary disease or other pathogenesis responsible for heart-block, either auriculoventricular or intraventricular, does not run parallel to gross lesions of the larger arterial stems of the coronary circulation, the obstruction of which produces clinical evidence of coronary disease in the form of myocardial infarction. Of special interest is the fact that intraventricular block was relatively almost as common in cases of angina pectoris without clinical coronary thrombosis (except perhaps as a terminal event) as in cases of clinical coronary thrombosis without angina pectoris. On the other hand the association of auriculoventricular and intraventricular block with coronary disease is frequent enough to be highly significant.

Furthermore, in our series the prognosis of older patients (over fifty years old) of heart-block, either auriculoventricular or intraventricular, is about equally unfavorable whether or not there are associated clinical evidences of coronary disease, that is, angina pectoris and coronary thrombosis.

In the instance of the sixteen patients with auriculoventricular block with angina pectoris or coronary thrombosis who died, the average age at the time of the discovery of the block was fifty-five years

and the average duration of life after the discovery of the block was twenty-two months, while the thirty-one patients with fatal auriculoventricular block without angina pectoris or coronary thrombosis recognized clinically, or other known etiological factors, averaged sixty years of age at the time of the discovery of the block and survived such discovery an average of thirteen months.

In the instance of the 54 patients with intraventricular (bundle-branch) block with angina pectoris or coronary thrombosis who died, the average age at the time of the discovery of the block was sixty-one years and the average duration of life thereafter eighteen months, while the 42 patients with fatal intraventricular (bundle-branch) block without angina pectoris or coronary thrombosis recognized clinically averaged sixty-one years of age at the time of the discovery of the block and survived such discovery nineteen months. There are a few individuals who survive many years and to old age with auriculoventricular or intraventricular block.

It may be concluded from this analysis that the coronary supply to the auriculoventricular node and bundle and its branches is not necessarily blocked as a result of the lesion (thrombosis or embolism) which blocks the coronary supply to the areas of the heart (anterior apical and posterior basal portions of the left ventricular myocardium) most commonly affected in clinical coronary thrombosis, but that such supply may be seriously involved by atherosclerotic or other processes with poor prognosis even when there is no associated angina pectoris or clinical evidence of sudden blockage of the anterior descending branch of the left coronary artery or of the main trunk of the right.

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THE USE OF ETHER IN MEASURING THE CIRCULATION TIME FROM THE ANTECUBITAL VEINS TO THE PULMONARY CAPILLARIES*

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DURING the past decade the circulation time in man has been studied intensively. Discussions of methods employed in these studies may be found in papers by Kisch,[1] Blumgart,[2] Tarr, Oppenheimer, and Sager,[3] and others. Essentially, all circulation-time methods consist of the introduction of a foreign substance into a peripheral systemic vein and the measurement of the time interval elapsing between the injection and the arrival of the fastest flowing particle at designated points in the circulation.

The signal reactions in such methods are either subjective or objective, depending upon the physical and pharmacological characteristics of the substance injected. Methods employing physical properties of substances as end points (fluorescein, sodium chloride, and radium emanation) are mainly objective, whereas methods using substances that evoke a specific pharmacological or physiological response are either subjective (calcium chloride, sodium dehydrocholate, and saccharin), or objective (carbon dioxide, histamine, and sodium cyanide). These methods have wide clinical applicability, but they present certain limitations since, with the exceptions of radium emanation and sodium cyanide, they fail to give more than indirect information as to the velocity of blood flow in component portions of the pathway traversed by the injected substance.

By the application of the radium emanation and sodium cyanide methods, attempts have been made in the past to study the blood velocity in selected segments of the circulation. Blumgart and Weiss[4] introduced radium emanation into a peripheral vein and with the aid of a detector determined its arrival at designated points in the pathway, measuring thereby the speed of flow in the peripheral ("arm to right heart" time) and pulmonary ("right heart to arm" time) circulation. Robb and Weiss[5] similarly employed small doses of sodium cyanide to obtain values for the "peripheral venous" segment, and for the "crude pulmonary time." Valuable as these methods are, they measure arbitrary rather then physiological segments of the circulation.

Until recently, no method had been described which permits the differentiation of the right and left heart circuits on a physiological or

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dynamic basis. At a meeting of the Society for Experimental Biology and Medicine held April 18, 1934, the author[6] described the ether method as an objective as well as a subjective method clinically applicable for measuring the circulation time of the pathway of the right heart unit. By the application of this method, the two sides of the heart with their respective afferent and efferent vessels may be studied as functional subdivisions of the vascular pathway which includes the pulmonary circuit.

The principle of the method consists of the intravenous introduction of a volatile substance and the measurement of the time that elapses before the odor characteristic of the injected substance is perceived by either patient or investigator. During this time interval the foreign substance passes through the peripheral venous segment, the right heart, and the pulmonary artery to the pulmonary arterial capillaries whence it volatilizes into the pulmonary alveoli. It then ascends with great rapidity through the air passages to the olfactory organ and is readily recognized. Among the volatile substances available for measuring the circulation time from the antecubital veins to the pulmonary capillaries, the author has found ether to be highly satisfactory, for the following reasons:

1. Its volatility at blood temperature is so great (ether boils at about 35° C.) that even when a small quantity is injected, the amount that volatilizes in the pulmonary capillaries during the first circuit of the blood is invariably sufficient to be perceptible by smell.
2. Only a small volume is needed. This permits rapid intravenous introduction so that the ether will flow in a small blood volume. The advantage of this is that it results in a sharp definition, not only of the time of injection, but also of the time of arrival in the pulmonary capillaries.
3. It gives no constitutional symptoms in the quantities used. In over 350 patients, some of whom had two and even three injections, no untoward systemic reactions were encountered. In a few instances, ether injections seemed to have a transient "beneficial" effect upon the circulation. This was occasionally observed in the patient with decompensated heart disease who stated that his "heart felt better" or that he "could breathe more easily" following the injection.
4. Because of its marked volatility, the measurement can be repeated as often as desired.
5. Paravenous infiltration causes no necrosis.

Although ether has certain definite advantages, it is still not the ideal substance. During its injection, the subject may be aware of a "creeping" sensation along the course of the vein. In about one-third of the patients, particularly in those whose circulation time is either near the upper limit of normal, or delayed, or in those whose antecubital veins are small, pain of a transient cramplike character may appear immediately following the injection. This may last a few moments, but it

rarely lasts over a minute unless the procedure is complicated by paravenous infiltration. In sensitive individuals as determined by the Libman[7] test, the pain appears to be of higher incidence and greater severity. Although it is usually confined to the site of injection, it frequently radiates along the course of the vein to the shoulder, and at times may conceivably be due to venous spasm rather than direct venous injury. A change in structure of the vein as determined by palpation may occur at the site of injection. This may vary from simple localized thickening to local thrombosis. In a series of 110 patients in whom the veins were carefully observed for a period of at least seven days, localized changes in the vein (thickening or thrombosis) occurred twenty-nine times, or in about 26 per cent of the cases. Except for the local change, this complication has never produced any untoward symptoms. In fact, one is usually unaware of its existence since it develops slowly and causes no pain, unless there has been paravenous infiltration. Pulmonary embolism has never been observed. Should a change take place in the structure of a vein, it is usually clinically recognizable from three to seven days after the injection. Its delayed appearance suggests a low grade chemical endophlebitis which incidentally may occur during the administration of other related volatile substances. For example, Vorzimer[8] obtained a high incidence of venous thrombosis following the use of acetone for circulation time studies. In his series, similar pathological changes in the veins also became manifest at the local site between the third and seventh day.

I. MATERIAL AND METHODS

A study was made of 352 individuals between the ages of sixteen and seventy-five years. Of this group, 272 were ward patients* suffering from various conditions, 52 were ambulant patients from the out-patient department, and 28 were normal young adults between the ages of fifteen and twenty-three years. In 164 there was no evidence of any circulatory disturbance, whereas in a group of 87 patients, the circulatory manifestations of either left or right or universal (left and right) heart failure were present.

The ether circulation time from the antecubital veins was determined in the entire group. In 8 patients it was also measured from the dorsal ankle veins. The saccharin circulation time and the venous pressure were measured in 158 patients of the series.

A. *The Measurement of the Circulation Time With Ether.*—The ether circulation time from an antecubital vein is determined by the following method: 5 minims (0.33 c.c.) of ether and 5 minims of normal saline are drawn into a 1 or 2 c.c. syringe to which a 20-gauge needle is attached. The mixture separates out into layers. The individual reclines in bed

*These patients were studied on the Medical Services of Dr. George Baehr and Dr. B. S. Oppenheimer, and on the Surgical Service of Dr. Harold Neuhof.

comfortably from about fifteen to twenty minutes. His arm is propped up to a level corresponding to the right auricle. He is familiarized at first with the odor of ether. He is then instructed to relax, breathe normally, and to announce when he smells the ether. It is advisable to forewarn the subject that he may experience momentary discomfort at the site of the venipuncture during the period of injection. A tourniquet is then applied, and the needle is inserted into a large antecubital vein. After waiting about a minute following the release of the tourniquet to allow local circulatory disturbances to subside, the investigator rapidly injects the mixture, taking only a fraction of a second for the procedure. The end point is sharp and unmistakable. Moreover, an observer in a position close to the subject can perceive the ether odor almost as rapidly as the patient. This objective confirmation, valuable as it is in itself, becomes of especial importance when studying unconscious or uncooperative patients. The time interval that elapses between the injection of ether and the registration of the end point is clocked with a stop watch and represents the circulation time of the pathway of the right heart unit. To yield results which will check closely on repetition, the subject must relax and must not hold his breath during the procedure, for this retards the venous return to the heart.

The ether circulation time from a dorsal ankle vein is determined in the same manner. The individual lies in the recumbent position. The chosen vein is raised to the level of the right auricle. The veins being of small caliber in this location, a hypodermic rather than a larger needle is preferable for the injection.

B. *The Measurement of the Circulation Time With Saccharin.*—For purposes of comparison with the ether circulation time, and for the derivation of the circulation time of the pathway of the left heart unit, the saccharin method of Fishberg, Hitzig, and King[9] was employed in a group of 158 patients. The procedure is essentially the same as that for the ether method. The end point, however, is a sweet taste at the back or tip of the tongue. In health, the saccharin circulation time ("arm to tongue" time) varies from 9 to 16 seconds. The sodium dehydrocholate (decholin) method of Winternitz, Deutsch, and Bruell,[10] recently studied by Tarr, Oppenheimer and Sager[3] was also employed in 8 normal patients of this series. The saccharin and decholin readings agreed very closely (within 1 to 2.5 seconds).

In a number of the cases studied earlier, delayed local thrombosis developed more frequently following the simultaneous or consecutive injections of ether and saccharin into the same vein at the same sitting. This also occurred in two of the patients who received decholin-ether injections. The incidence of this complication may be considerably lessened by employing separate veins for the injections when saccharin or decholin is used in conjunction with ether.

C. *The Measurement of the Venous Pressure.*—The venous pressure was determined by a slight modification[11] of the direct method of Taylor, Thomas, and Schleiter.[12] Normal measurements with this method vary between 4 and 8 cm. of blood. Readings were of value in selected cases in determining the presence or absence of circulatory disturbances and in corroborating the clinical impressions of either left or right heart failure.

Except for general implications, the correlation of the venous pressure with the ether and saccharin circulation times will not be presented in this paper. A later publication on the venous pressure by Dr. Arthur M. Fishberg and the author will include such a study.

II. NORMAL CIRCULATION TIME VALUES

A. *The Normal (Ether) Circulation Time From the Antecubital Veins to the Pulmonary Capillaries. Measure of the Right Heart Unit (Arm-to-Lung Time).*—In 164 "normal" subjects in whom there were no manifest circulatory disturbances, the ether circulation times were distributed as shown in Table I.

TABLE I

"ETHER TIME" FROM ANTECUBITAL VEINS TO PULMONARY CAPILLARIES

CIRCULATION TIME (SEC.)	NUMBER OF INDIVIDUALS
3.5-3.75	9
4.0-4.75	40
5.0-5.75	39
6.0-6.75	42
7.0-7.75	23
8.00	11
Total	164

The end point was definite in practically every case, only an occasional measurement requiring repetition. Repeated injections in a series of 22 patients agreed either exactly or within from 0.5 to 2 seconds. Readings of 8.5 to 9.5 seconds were occasionally obtained when the end point was recorded only subjectively. After reexamination of these patients objectively to exclude local olfactory disturbances, the circulation times usually fell below 8 seconds.

The mean ether circulation time derived from the data in Table I is 5 54 seconds and the standard deviation is 1.25 seconds. As commonly interpreted by statisticians this would mean that 95 per cent of all normal cases will show a circulation time of from over 3 to 8 seconds or that more than two-thirds of all normal cases will show a circulation time between 4.3 and 6.8 seconds. The range actually varied from 3.5 to 8 seconds.

An analysis of our normal series reveals no apparent relationship between the "ether time" and the age, sex, or venous and arterial pres-

sures. Similarly, no correlation can be established between the ether time and the slight fluctuations in pulse rate which varied in our patients during the period of examination from 70 to 96 beats per minute. In 5 children between the ages of seven and eleven years, not included in the above series, the ether time was faster, ranging between 2.5 and 5.5 seconds.

The quantity and physical state of the injected ether evidently bear important relationships to the accuracy of the ether circulation time. A relationship of the amount of injected ether to the ether time was recognized following the separate introduction of 0.33 c.c. and 0.15 c.c. of ether into a group of 8 patients and comparing results. In each instance, not only was the end point with the smaller dose less defined, but the circulation time showed a prolongation of from 1.5 to 3 seconds. The delay as well as the lessened acuity of the end point were even more marked when 0.15 c.c. of ether was dissolved in 3 c.c. of saline and injected into the same group of 8 patients. The prolongation of the circulation time in the latter instance may be attributed, first, to an increased volume which requires a longer injection time; second, to the use of dissolved ether which apparently volatilizes less completely and less readily in the pulmonary capillaries than ether not in solution; and third, to the lower pressure gradient of the ether in the alveoli when smaller quantities of the substance are employed.

To prove that the pressure gradient of ether in the pulmonary bed is adequate when 0.33 c.c. (5 minims) of ether is employed, this quantity (0.33 c.c.) and double this quantity (0.66 c.c.) were injected separately into a group of five patients and the results compared. Although the end point was sharper following the larger dose, the ether time was not significantly accelerated.

TABLE II

COMPARISON OF ETHER TIMES OBTAINED WITH 0.33 C.C. AND 0.66 C.C. OF ETHER

CASE NO.	ETHER TIME (0.33 C.C.) SEC.	ETHER TIME (0.66 C.C.) SEC.
1	6.0	5.0
2	4.5	4.5
3	7.0	6.0
4	7.5	6.0
5	5.0	4.5

A quantitative relationship between rate of respiration and the ether time undoubtedly exists. Such a relationship was also found by Fishberg, Hitzig, and King in their saccharin studies. Rapid breathing will hasten the venous return to the right heart and thereby accelerate the circulation time, whereas slow breathing will retard the venous return and prolong the circulation time. In a small group of patients whose "ether times" were near the upper limit of normal (6 to 8 seconds),

rapid breathing (40 per minute) caused an acceleration of blood flow of 1 to 2.5 seconds, whereas in patients with "ether times" of 4 to 6 seconds, the acceleration, if present, did not exceed 0.5 to 1.5 seconds.

Strictly speaking, the ether time includes not only the time which elapses during the passage of ether from the antecubital veins to the pulmonary capillaries, but also the interval required for its flow through the tracheobronchial system to the nose. However, because of the rapidity with which a light gas diffuses in a gaseous mixture, it may be assumed that the time required for the ether to flow from the pulmonary alveoli to the nasopharynx is negligible in comparison with the actual circulation time. Hence, for practical purposes, the pulmonary arterial capillaries may be regarded as the site of the ether end point.

The question arises whether the phase of the respiratory cycle during which the injected ether is discharged into the lungs affects the circulation time. The speed of passage of ether from the alveoli to the olfactory organ will depend primarily on the pressure gradient of ether at the pulmonary bed. If this pressure gradient is assumed to be adequate, the modifying factors involved consist of the to-and-fro movements of air during inspiration and expiration. From a theoretical consideration of the law of diffusion of gases and of the normal velocity of air during the two phases of the respiratory cycle, it is clear that the diffusion of ether will offset to a varying extent any retardation due to inspiration or any acceleration due to expiration.

B. *The Comparison of the Normal Ether to the Normal Saccharin Circulation Time.*—Of particular interest is the comparison of the ether time, which is a measure of the circulation time from the antecubital veins to the arterial capillaries of the lung, with the "saccharin time," which determines the speed of the circulation from the antecubital veins through the lungs to the capillaries of the tongue. In a consecutive group of fifty-two normal subjects the percentage relationship of ether time to saccharin time showed the following variations:

TABLE III

PERCENTAGE RELATIONSHIP OF NORMAL ETHER TIME TO NORMAL SACCHARIN TIME

ETHER TIME EXPRESSED AS % SACCHARIN TIME	NUMBER OF INDIVIDUALS
33-39	6
40-49	32
50-59	12
60-66	2

This study shows that in 44 (84 per cent) of the 52 normal patients, the ether time was from 40 to 59 per cent of the saccharin time. In 32 individuals (61 per cent) the ether time was from 40 to 49 per cent of the saccharin time. A comparison of the extreme limits of normal ether time (3.5 to 8 sec.) with those of normal saccharin time (9 to

16 sec.) shows a 39 per cent relationship existing at the lower limit of normal and a 50 per cent relationship at the upper limit of normal.

C. *The Normal Circulation Time From the Pulmonary Capillaries to the Capillaries of the Tongue as Measured by the Saccharin Time–"Ether Time" Difference. Measure of Left Heart Unit (Lung-to-Tongue Time).* —By subtracting the ether time which is a measure of the right heart unit, from the saccharin time which measures the circulation time from the antecubital veins to the lingual capillaries, the circulation time of the left heart unit, i.e., from the pulmonary capillaries to the capillaries of the tongue, may be obtained. This may be designated as the saccharin time–ether time difference. Although the difference between the maximum saccharin time (16 sec.) and the maximum ether time (8 sec.) is 8 seconds, the saccharin time–ether time difference in the fifty-two normal subjects varied between 4.5 and 9.5 seconds. Consequently, one may conclude that in a normal individual the maximum time required for a foreign substance to pass from the capillaries of the lung to the capillaries of the tongue or to traverse the pathway of the left heart unit will usually not exceed 9.5 seconds. Such a maximum difference was recorded in only four individuals of the normal series. This quantitative relationship of the ether time to the saccharin time, that is to say, the saccharin time–ether time difference, becomes of particular importance in the study of patients with circulatory disturbances.

D. *The Normal Ether Circulation Time From the Dorsal Ankle Vein to the Pulmonary Capillaries.*—The circulation time from the dorsal ankle vein to the pulmonary capillaries was recorded in eight normal patients. The end point was sharp in every case. The series is, however, too small to allow conclusions as to the limits of normal.

TABLE IV

ETHER TIME FROM ANTICUBITAL AND DORSAL ANKLE VEINS TO PULMONARY CAPILLARIES

CASE NO.	FROM ANTECUBITAL VEIN (SEC.)	FROM DORSAL ANKLE VEIN (SEC.)
1	8	18
2	6	24
3	5	30
4	7	23
5	6	20
6	7	34
7	6	30
8	5	16

In this group the ether time varied from 16 to 34 seconds. Many factors probably affect the circulation time from the lower extremity, namely, the age and height of the individual, the tortuosity of the veins of the lower limb, and the intraabdominal pressure.

Because of wide fluctuations of the normal ether circulation time from the dorsal ankle veins, this procedure has limited application. Com-

parative determinations from both lower limbs may be of value, however, in cases of unilateral edema or venous obstruction. This is well illustrated by observations in the following case.

Case.—A fifty-year-old female, following a febrile illness, developed massive enlargement of her left lower extremity six months before she came under our observation. With the exception of the tense pitting edema which extended upward to the inguinal region, she was in good physical condition. The differential diagnosis rested between venous and lymphatic obstruction.

The ether circulation times from the ankle veins of both limbs and the venous pressures in both femoral veins were determined above the area of edema (4 cm. below the inguinal ligament). The results are given in Table V.

TABLE V

LOWER EXTREMITY	ETHER TIME (ANKLE) (SEC.)	VENOUS PRESSURE (FEMORAL) (CM. OF BLOOD)
Right	17.5	6.0
Left	34.0	20.5+*

*Blood clotted in manometer at this level.

A comparison of the ether times and venous pressures shows conclusively the presence of venous obstruction above the left femoral vein probably due to an old thrombophlebitis of either the left common or the left external iliac vessel. Coexisting lymphatic obstruction, however, could not be excluded.

III. CIRCULATION TIMES IN HEART FAILURE

A. *Failure of the Left Side of the Heart.*—The subject of circulation times in failure of the left side of the heart was noted by Hitzig[6] and has been discussed at length by Hitzig, King, and Fishberg.[13] Their study reveals that in most instances of left ventricular failure, whether due to hypertensive, arteriosclerotic, syphilitic, or rheumatic heart disease, the ether time may be within normal limits, but the saccharin time may be much prolonged. The resulting abnormal increase of the saccharin time–ether time difference suggests that the retardation of blood velocity in such instances is localized to the pathway of the left heart unit or to that portion of the arm-to-tongue circulation which is beyond the pulmonary arterial capillaries (lung-to-tongue segment). The normal systemic venous pressure and the normal ether time testify unequivocally to the functional efficiency of the right ventricle. In other cases, however, even though the venous pressure remains within normal limits, the ether time may be moderately prolonged, occasionally to 14 seconds. This may occur particularly when the left ventricular insufficiency is severe and the pulmonary engorgement pronounced. The abnormal ether and saccharin times point to retardation of blood velocity

in both the arterial and venous portions of the pulmonary circuit. As a rule, the saccharin time–ether time differences in such instances also show disproportionate prolongation indicating that in these cases the rate of pulmonary blood flow is also predominantly slowed in the segment beyond the pulmonary arterial capillaries. The prolongation of the ether time in left ventricular failure may really be regarded as a manifestation of "incipient" failure of the right side of the heart. It reveals that although the right ventricle is able to maintain a normal systemic venous pressure, it is unable, laboring as it is against an increased pulmonary resistance (hypertension of pulmonary circuit), to maintain the normal blood velocity through its circulatory pathway. As has been mentioned by Hitzig, King, and Fishberg, normal circulation times are occasionally encountered in left ventricular failure. This was also recently observed in a case of malignant hypertension in which the venous pressure was 6 cm. of blood, the ether time was 6.5 seconds and the saccharin time was 13.5 seconds.

B. *Failure of the Right Side of the Heart.*—When the general venous pressure is elevated because of intrinsic functional or organic disease of the heart, the ether circulation time, except in occasional cases, is prolonged. Such prolongation appears to be proportional to the degree of myocardial insufficiency, or roughly to the height of the venous pressure. The ether times in eighteen cases of frank right heart failure which were of rheumatic, syphilitic, and arteriosclerotic etiology varied from 9 to 27 seconds. The saccharin times were correspondingly or disproportionately prolonged. The saccharin time–ether time differences were either within normal limits or slightly or markedly increased. They ranged from 9 seconds (upper limit of normal) to as high as 32 seconds. The variation in the lung-to-tongue time appears to be related to the degree of pulmonary congestion. Of interest in this regard are two cases with contrasting clinical pictures which exhibit the above extremes in the saccharin time–ether time difference. The circulatory disturbance in one case suggested at first the possibility of primary right heart failure. The venous pressure was 26 cm. of blood; the ether time was 17 seconds, the saccharin time was 26 seconds; and the saccharin time–ether time difference was 9 seconds. This patient had marked cyanosis, no dyspnea in bed, very little, if any, orthopnea, and no clinical signs of pulmonary engorgement. There was peripheral edema, but no hydrothorax. Post-mortem examination revealed extensive coronary artery disease with recent thrombosis of the right posterior descending branch and myomalacia of the posterior wall of the left ventricle and septum. In the second patient, who also suffered from severe coronary artery disease with recent thrombosis, the extreme slowing of pulmonary blood flow which occurs most strikingly in association with failure of the left ventricle was well illustrated by the following measurements. The venous pressure was 22 cm., the ether time was 26 seconds; the saccharin time was 58 sec-

onds; and the saccharin time–ether time difference was 32 seconds. Clinically, he was acutely ill, cyanotic, dyspneic, and orthopneic at rest, and he presented signs of marked pulmonary engorgement. He had bilateral hydrothorax for which he was tapped on several occasions. At post-mortem examination severe coronary artery disease, recent thrombosis of the left circumflex and right coronary arteries, and myomalacia of both ventricles were found. Ascites was also present. From these clinical, circulatory, and anatomical observations it may be said that although in each case both ventricles were functionally incapacitated due to the same disease process, the dynamic disturbance was chiefly right-sided heart failure in the first case, and predominantly left-sided heart failure in the second case. Since both patients had almost identical venous pressures, it is interesting to correlate the clinical pictures with the enormous variations in the lung-to-tongue time. Since the lung-to-tongue time appears to be a rough index of the extent of congestion in the venous segment of the pulmonary circuit, the absence of hydrothorax in the first patient and its occurrence in the second patient suggest a possible relationship between the genesis of this condition and the degree of prolongation of the saccharin time–ether time difference.

True cases of "isolated" primary right heart failure were not observed.

C. *Heart-Block.*—Four patients with heart-block and accompanying bradycardia were studied. In one patient with partial heart-block and a pulse rate of 45, the ether and the saccharin times were within normal limits. In another patient with complete block and a bradycardia of 32, the lung-to-tongue time, as manifested by a saccharin time–ether time difference of 17.5 seconds, was considerably slowed. The ether time and the saccharin time were 7.5 and 25 seconds, respectively.

In two cases of complete heart-block with bradycardias which fluctuated between 28 and 35, both the ether time and the saccharin time were abnormally delayed. Despite the presence of normal venous pressures and compensatory arterial pressures (systolic hypertension and high pulse pressure), the ether times were 10.5 and 12.5 seconds and the saccharin times were respectively 29 and 32 seconds. In both of these cases, the high saccharin time–ether time differences indicated disproportionate prolongation of the lung-to-tongue time. The retardation of pulmonary blood flow in these cases may be attributed not only to the left ventricular insufficiency but also to the profound slowing of the heartbeat.

IV. CIRCULATION TIMES IN INTRATHORACIC DISEASES

A. *Mediastinal Tumor With Superior Vena Cava Syndrome.*—In two patients suffering from mediastinal tumor with local elevation of the venous pressure, the ether time was high normal (7.5 and 8 sec.),

whereas in a third patient it was slightly retarded (10 sec.). Readings obtained with saccharin showed corresponding alterations of the saccharin time, but the saccharin time-ether time difference was within normal limits in all three cases. Observations with saccharin alone were made by Fishberg, Hitzig and King[14] in a fourth patient who presented a classical superior vena cava syndrome due to mediastinal Hodgkins disease. Despite an elevation of the venous pressure to about 32 cm., the saccharin time was 14 seconds from one antecubital vein and 18 seconds from a corresponding vein on the other arm.

Although the velocity of blood flow in the peripheral venous segment is probably retarded by a mediastinal tumor which causes stasis in the large systemic veins, the ether time may still remain within normal limits. As previously stated, the ether time in patients with right heart failure is usually prolonged to a degree which parallels the elevation of the systemic venous pressure. With a venous pressure elevation in right heart failure comparable to that usually obtained in mediastinal tumor, the circulation times with ether and saccharin would be considerably retarded. This observation indicates that the slowing of the ether circulation time occurs most markedly when the circulatory disturbance involves the entire pathway rather than only the peripheral venous segment of the right heart unit.

B. *Pleuropulmonary Diseases.*—The ether and saccharin circulation times were determined in a large group of patients who suffered from a variety of diseases involving the lungs and pleurae. The diseases studied included pneumonia, pleurisy with effusion, bronchial asthma, bronchiectasis, and pulmonary tuberculosis. The determinations were within the limits of normal except in occasional patients in whom the clinical picture was complicated by myocardial insufficiency and an elevated venous pressure.

C. *Unilateral Functioning Lungs.*—It is common knowledge among clinicians that the circulatory dynamics are only rarely disturbed in pulmonary conditions with single functioning lungs. This fact is substantiated objectively by circulation time studies which reveal conclusively that in such cases the velocity of blood flow through the lungs is almost never retarded. For example, in two cases of unilateral tension pneumothorax, in which there was moderate cyanosis and slight elevation of the venous pressure due probably to compression of the mediastinal veins, the ether and saccharin times were normal. Normal circulation times and venous pressures were recorded in four patients with massive unilateral pleural effusions of the idiopathic type despite the moderate shifting of the mediastinum to the unaffected side. Normal circulatory measurements were also obtained in a case of obstruction of the main bronchus with massive unilateral atelectasis, despite the presence of a moderate degree of cyanosis.

Circulatory studies were also carried out in conjunction with Dr. Harold Neuhof in eight patients with extensive unilateral disease of the lungs.

TABLE VI

CASE NO.	PULSE (PER MIN.)	RESPIRATION (PER MIN.)	VENOUS PRESSURE (CM.)	ETHER TIME (SEC.)	SACCHARIN TIME (SEC.)
1	96	22	4.0	2.75	
2	88	20	3.5	3.00	7.0
3	92	20	5.0	3.00	7.5
4	98	18	4.5	4.00	8.5
5	86	22	4.0	3.50	
6	88	20	5.5	4.00	10.0
7	94	20	3.5	3.00	
8	100	20	4.0	4.00	8.5

Although one lung was functionally eliminated by disease or operation or both, the venous pressures in this series ranged between 3.5 and 5.5 cm. and the ether times fell between 2.75 and 4 seconds. The saccharin times in five of these patients varied between 7 and 10 seconds. Three of these patients showed a faint degree of labial cyanosis. The above findings may be indicative of an accelerated pulmonary blood flow which may result from mechanisms compensating for the diminished aerating surface of the lungs.

IV. CIRCULATION TIMES IN BLOOD DISEASES

A. *Polycythemia.*—In two patients suffering from uncomplicated polycythemia vera, the ether time and the saccharin time were proportionately prolonged. In a third patient the circulation times were normal. The venous pressures were normal in all cases.

TABLE VII

CASE NO.	CIRCULATION TIMES IN POLYCYTHEMIA VERA	
	ETHER TIME	SACCHARIN TIME
1	11.5	21
2	12.0	22
3	7.5	16

B. *Anemia.*—The ether times in five cases of secondary anemia were between 3.5 and 4.5 seconds while the saccharin times varied between 8 and 11.5 seconds. In one case of pernicious anemia, the ether time was 6.5 seconds and the saccharin time was 14 seconds.

V. THYROID DISEASE

A. *Graves' Disease.*—This subject has been studied extensively by Blumgart and by Tarr, Oppenheimer and Sager. In a series of six patients observed by the author, the ether circulation times ranged between 3 and 4.5 seconds, whereas the saccharin times varied between 7 and 9.5 seconds.

B. *Postoperative Hypothyroidism.*—Cases of true myxedema were not observed. However, in three patients whose basal metabolic rates following subtotal thyroidectomy fluctuated between minus 20 and minus 30 per cent, ether times ranging between 7 and 8.5 seconds were obtained. The saccharin times were also near the upper limit of normal.

VI. MISCELLANEOUS CONDITIONS

Normal ether circulation times were also obtained in a variety of other clinical conditions in which there was no evidence of any coexisting circulatory disturbance. These included acute and chronic nephritis, nephroses, and cirrhosis of the liver.

COMMENT

The ether time, which measures the speed of blood flow from the antecubital veins to the pulmonary capillaries, serves as an index of the functional capacity of the right heart. Similarly the saccharin time–ether time difference determines the functional capacity of the left heart. With the exception of polycythemia vera in which there may also be universal retardation of the velocity of blood flow, the ether time appears to be normal in all noncardiac conditions that have been studied. Elevation of the venous pressure in the large systemic veins, unless caused by functional insufficiency of the right ventricle, is rarely accompanied by a significant prolongation of the ether time. This impression is based upon the findings in cases of mediastinal tumor and tension pneumothorax. Another interesting observation on this point was made in a patient who had unilateral elevation of the venous pressure (21 cm.) due probably to axillary or subclavian vein thrombosis with suspected partial recanalization. The ether time in that arm was 7.5 seconds. In the opposite arm where a venous pressure of 7 cm. was obtained, the ether time was 5.5 seconds. This shows that although there was a retardation of 2 seconds as compared with the sound side, the ether time on the abnormal side was still within the normal range.

Prolongation of the ether time and of the saccharin time–ether time difference occurs not only in frank right heart failure but also in left ventricular failure when the functional capacity of the right ventricle becomes insufficient to master the increased resistance in the pulmonary circuit. Although in these cases the prolonged ether time offers the only evidence of insufficiency of the right ventricle, this circulatory derangement is indicative of incipient failure of the right heart despite the presence of a normal venous pressure. There are also occasional cases of frank right heart failure secondary to antecedent left ventricular failure, in which the saccharin time–ether time difference may remain within the normal range, even though the ether and saccharin times are retarded. These findings are compatible with the well known clin-

ical concept, recently emphasized by Fishberg,[15] that the pulmonary congestion associated with left ventricular failure may often be considerably lessened upon the advent of right heart failure.

The comparative study of the ether and saccharin times in various types of heart failure is of value in localizing the portion of the circulation in which blood flow is retarded. By the combined application of these methods, evidence has also been obtained which offers convincing support to the "backward failure" theory of heart failure. At the suggestion of Dr. Ernst Boas, interesting observations in this regard were recently made in a case of essential hypertension with progressively developing heart failure. When first seen, this patient presented the classical syndrome of left ventricular failure. The venous pressure was 7 cm. of blood, the ether time was 7 seconds, and the saccharin time was 23 seconds. Two weeks later the venous pressure was essentially unchanged, but the ether time was 9 seconds and the saccharin time was 28 seconds. Gradually, within a period of three weeks thereafter, the usual phenomena of right heart failure became manifest. The venous pressure rose to 17 cm. of blood; the ether time was 16 seconds; and the saccharin time was 30 seconds. After a period of bed rest, digitalization, and diuresis, the venous pressure fell to 9 cm. of blood; the ether time was 8 seconds; and the saccharin time was 20 seconds. The measurements repeated prior to discharge, two weeks later, showed a venous pressure of 6.5 cm. of blood, an ether time of 7.5 seconds, and a saccharin time of 18 seconds.

SUMMARY

1. Ether introduced intravenously may be used as a subjective and objective method for the determination of the circulation time from the antecubital veins to the pulmonary capillaries (arm-to-lung time). The ether time serves as a measure of the functional capacity of the right heart unit.

2. A study was made of 352 individuals. In 164 "normal" adults, the ether time from the antecubital veins varied between 3.5 and 8 seconds. The ether time from the dorsal ankle veins in 8 adult individuals ranged between 16 and 34 seconds.

3. The percentage relationship of ether time to saccharin time ranged from 33 to 66 per cent in 52 normal individuals.

4. The saccharin time–ether time difference, which is an indirect measure of the circulation time from the pulmonary arterial capillaries to the capillaries of the tongue (lung-to-tongue time), may serve as an index of the functional capacity of the left heart unit. The range in 52 normal subjects was 4.5 to 9.5 seconds.

5. Prolongation of ether time usually occurred in right heart failure, in certain instances of left heart failure with incipient right heart failure, in heart-block, and in polycythemia vera.

6. The ether time in three cases of mediastinal tumor with compression of superior vena cava was either high normal or only slight retarded, despite the elevation of the venous pressure in the large systemic veins.

7. In all other clinical conditions uncomplicated by insufficiency of the right heart, the ether time was usually within normal limits.

8. Ether and saccharin circulation times in conditions associated with unilateral functioning lungs are either extremely rapid or within the lower limits of normal. The accelerated pulmonary blood flow may be an expression of mechanisms operating to compensate for the diminished aerating surface of the lungs.

9. A comparison of the ether and saccharin time is of value in localizing the segment of the circulation in which blood flow is retarded.

10. Evidence obtained by the ether and saccharin methods supports the "backward failure" theory of heart failure.

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Department of Clinical Reports

A CASE OF PULSATING SPLEEN IN MITRAL AND TRICUSPID DISEASE*

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MANGES[1] was the first to report a case of pulsating spleen in mitral and tricuspid disease. Except for the following case, no instance of pulsation of the spleen has been observed in the large number of cases seen in the Cardiac Follow-up Clinic of Cook County Hospital.

An Italian girl, seventeen years of age, was referred to the cardiac clinic on March 31, 1931, following her discharge from the hospital. The only serious illness in her past history was scarlet fever in 1927; however, in February, 1931, dyspnea, edema and precordial pain were noticed. A month later, at her first visit to the clinic, she was observed to be a well-nourished girl, with normal temperature, but with a regular tachycardia of 120 per minute.

Inspection revealed a diffuse apex impulse in the anterior axillary region, accompanied by a systolic retraction. Neither cyanosis nor edema was present. A distinct presystolic thrill was easily felt over the precordium, in addition to the shock due to closure of the pulmonic valves.

Percussion, confirmed by a teleroentgenogram, gave the outline seen in Fig. 1. The heart area extended 12 cm. to the left of the midline and 6 cm. to the right, with a cardiothoracic ratio of 0.70. Systolic, presystolic, and middiastolic mitral murmurs were heard, as were the usual moist râles in the bases of the lungs. A positive Wassermann reaction was interpreted as being due to a congenital syphilis. At this time neither the liver nor the spleen was palpable.

Her condition improved until August, 1931, when an auricular fibrillation was first observed. In May, 1932, she was referred to the hospital because of congestive heart failure, at which time only the liver was palpable. On her return to the clinic, three months later, she was found to have developed a tricuspid insufficiency, as evidenced by the enlarged, pulsating liver, and positive venous pulsation in the veins of the neck. At the same time there was felt a large spleen, extending to the crest of the ileum, with definite expansile pulsation. Other clinicians in attendance have confirmed these observations.

At present her condition is unaltered, her blood pressure as heretofore being 120 mm. systolic and 70 mm. diastolic. The pulsations of both liver and spleen have shown no change since August, 1932. Following the oral administration of hippuran, the outlines of the kidneys, liver, and spleen were plainly visible, as verified by Dr. Roger Vaughn, who interpreted the x-ray pictures. Simultaneous tracings of the hepatic and splenic pulsations were recorded upon the electrocardiogram, Lead II. The pulsations recorded in the spleen are unquestionably simultaneous

*From the Cardiac Follow-up Clinic at Cook County Hospital.

with those of the liver. The illustration (Fig. 1) is a photograph of the outlines of the heart, the liver, and the spleen. The cardiac outline is the result of superimposing the 2 meter cardiac shadow upon the chest.

DISCUSSION

According to Manges,[1] Nicholas Tulpius, of Amsterdam, in 1652 reported the first observation of pulsation of the spleen. Gerhardt, in 1882, reported three cases, all in patients with aortic insufficiency. In two, the splenic pulsation was observed during attacks of lead colic, the pulsations disappearing with recovery from the colic. In the third case, pulsation was coincident with the development of pericarditis. In 1887, Prior reported two cases, one in a patient with aortic insufficiency, the splenic pulsation appearing during an attack

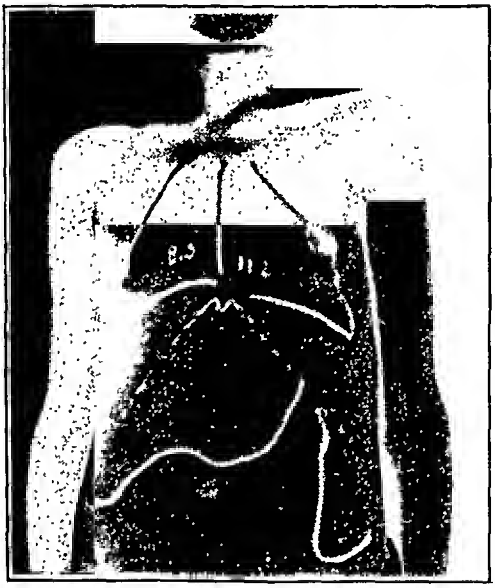

Fig. 1.—Showing the outline of the heart traced on the chest from the last 2 meter heart plate. The liver and spleen were palpated and outlined as shown.

of typhoid fever. The second patient had a marked dilatation of the left ventricle, and the pulsating spleen was noted during the course of a croupous pneumonia. Drasche, in 1888, observed pulsation of the spleen during an attack of pneumonia in a patient with aortic insufficiency. Sailer[2] observed pulsation of the spleen in a patient with aortic insufficiency, during the course of a terminal bacterial endocarditis.

There have been, therefore, nine instances of the observation of this condition, six of which were reported between the years of 1882 and 1888. Manges says that he looked for a second case for the next six years, and we have kept it in mind during the past three years, but thus far we have not encountered a second case. All the cases reported, except that of Manges, who found a pulsating spleen in mitral

and tricuspid disease, have been observed in the presence of aortic insufficiency. Our patient has never shown any evidence of aortic insufficiency. In the light of the cases reported thus far, there would appear to be four possible explanations for such a condition:

1. In aortic insufficiency there is probably a direct transmission of pulsations to the arteries of the spleen.

2. Transmission of the pulsations from the pulsating liver. Mechanically, the impulse produced in the vena cava by tricuspid insufficiency would have to pass through the capillaries of the liver into the portal veins and then into the splenic vein. This appears to us to be improbable, as it does also to the anatomists whom we have consulted. Nevertheless, such an explanation cannot be entirely disregarded.

3. That there is an anomalous communication between the splenic vein and the inferior vena cava. Such a communication with the vena cava would permit of the direct transmission of the impulse to the splenic vein, as it is transmitted to the hepatic vein in liver pulsation. Shepherd[3] reports that there is a specimen in the museum at McGill University in which there is a large anastomosis between the renal and splenic veins.

4. An arteriovenous communication involving the splenic vein. When one considers the anatomy of the venous sinuses of the spleen this would appear to be the only possible explanation.

Unfortunately, so far as is known, none of the cases reported came to autopsy. However, the extreme rarity of pulsating spleen makes it probable that it can be due only to one of the latter anomalies. In our opinion the most likely cause of a pulsating spleen in mitral disease and an intact aortic valve is the presence of an anomalous communication between the splenic vein and the vena cava.

SUMMARY

A case of pulsation of the spleen in mitral and tricuspid disease is reported, supplementing the single case thus far reported (by Manges). Eight cases of pulsating spleen occurring in aortic insufficiency have been reported by others.

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1. Manges, Morris: Pulsating Spleen in Mitral and Tricuspid Disease, Am. J. M. Sc. 154: 72, 1917.
2. Sailer, Joseph: Pulsating Spleen in Aortic Insufficiency, Am. Heart J. 3: 447, 1928.
3. Shepherd, Francis J.: Anomalies of the Veins, Reference Handbook of Medical Science, Vol. 8, p. 206, New York, 1908, William Wood & Company.

Society Transactions

AMERICAN HEART ASSOCIATION, 1935

The eleventh annual scientific session of the American Heart Association was held on June 11, 1935, at the Hotel Claridge, Atlantic City, N. J., with Dr. John Wyckoff as presiding officer. The following program was presented.

Program

The Duration of Life Following Initial Attack of Heart Failure. J. Murray Steele, M.D., New York, N. Y.

ABSTRACT

A numerical survey of cardiac patients admitted to the Hospital of the Rockefeller Institute for Medical Research between January, 1920, and December, 1932, is presented. Only those individuals, 154 in number, who suffered at some time from symptoms of heart failure at rest and whose records continued until death or up to January, 1935, were included in the study.

Of the 154 patients, 66 suffered from heart disease of rheumatic origin, 61 of arteriosclerotic and hypertensive origin, 9 of syphilitic origin, and 18 of unknown origin. The more clearly defined differences in behavior between the larger groups (rheumatic and arteriosclerotic) may be briefly pointed out. Duration of life as well as ability to work after the first attack of heart failure was longer in the individuals whose disease was rheumatic in nature (3.2 and 1.5 years, respectively) than in those whose difficulty was dependent upon arteriosclerosis or hypertension (2.6 and 1.1 years, respectively). It appeared also that the individuals in both groups whose auricles were fibrillating survived for a considerably longer period of time (3.5 years) than did those whose rhythm was normal (1.8 years). The difference in duration of life in the two groups may be due in part to the fact that the rheumatic group was much younger (36.7 years each) than the arteriosclerotic (59.3 years), and in part to the fact that the proportion of cases of auricular fibrillation was much greater in the rheumatic group (3:1) than in the arteriosclerotic (1:1).

In the whole group of 154 patients the average duration of life from the onset of the first attack of heart failure was 2.9 years. The yearly decrease in the number of patients alive following the first attack was found to be proportional to the number of living patients, approximately one-fourth dying each year. Three-fourths of the original group of patients sustained a second attack of heart failure at rest. It is of especial interest that the yearly decrease in number of patients living following a second attack of heart failure was also a logarithmic curve and that approximately the same proportion, one-fourth of the surviving patients, died each year. The suggestion is, naturally, that heart failure, unless fatal, does not alter to any great extent the subsequent length of life. The group of patients who suffer at least two attacks of heart failure are also interesting because they comprise that large class often labelled "chronic cardiac" which presents complex problems in treatment and its evaluation and serves generally as material for comparison of new and special methods of treatment with the usual forms of medical care—rest, restriction of fluids, and the administration of diuretics and digitalis.

The Results of Treatment in Cardiovascular Syphilis. Paul Padget, M.D., and Joseph Earle Moore, M.D., Baltimore, Md. See page 1017.

The Significance of Electrocardiographic Changes in Diphtheria. E. A. Burkhardt, M.D., Cary Eggleston, M.D., and Lawrence Smith, M.D., New York, N. Y.

ABSTRACT

This study concerns the relation of the onset of the disease to the occurrence of manifest changes in the electrocardiogram. Alterations in conduction and in the form of the ventricular complexes are described; the effects of therapy and the clinical manifestations are discussed.

The Pathological Analysis of Diphtheritic Myocarditis With Especial Reference to Electrocardiographic Findings. Lawrence Smith, M.D., E. A. Burkhardt, M.D., and Cary Eggleston, M.D., New York, N. Y.

ABSTRACT

The pathological findings in one hundred fatal cases of diphtheria are described. In many cases there appears to be a rough parallelism between the degree of change of conductivity, as measured by the electrocardiograph, and the severity of the anatomical changes. The alterations noted in certain protracted cases suggest that diphtheritic myocarditis should be considered as a cause of secondary heart disease a little later in life.

Peripheral Venous Phenomena in Congestive Heart Failure. William J. Kerr, M.D., San Francisco, Calif.

ABSTRACT

In the presence of right heart failure the tricuspid valve becomes incompetent, the venous pressure is elevated, and the liver becomes obviously distended. Under these circumstances the positive jugular pulsation following contraction of the right ventricle is propagated widely and under suitable manipulation can be described in the veins of the forehead, arms, hands, and legs. It is a stasis wave which travels along a distended vein.

The Relationship of Blood Pressure, Peripheral Vasomotor Activity, and Environmental Temperature. Ashley W. Oughterson, M.D., New Haven, Conn.

ABSTRACT

In this study a variety of patients was observed under conditions of controlled temperature and humidity. Blood pressure readings were correlated with peripheral skin temperatures while influenced by different levels of environmental temperature and humidity. It was found that in some individuals with hypertension the blood pressure could be raised as much as 100 mm. Hg on changing environmental temperature and humidity. The elevation of blood pressure was accompanied by a peripheral vasoconstriction. Older patients with a less elastic vascular bed did not show such marked changes. Normal subjects also showed little or no response to changes in environmental temperature and humidity. These observations suggest that certain individuals are hypersensitive to changes in environmental temperature and humidity.

The Influence of the Heat Regulatory Mechanism on Raynaud's Disease. Herman E. Pearse, Jr., M.D., Rochester, N. Y. See page 1005.

Observations Upon Electrocardiographic Tracings Obtained by the Use of Esophageal Leads in the Human Subject. W. Hurst Brown, M.D., Baltimore, Md.

ABSTRACT

The method is described, and the curves obtained are contrasted with standard and chest leads. The characteristics of the curves of the auricular complex are analyzed in both health and disease. Examples of auricular extrasystoles, flutter and fibrillation, and of sinus standstill and heart-block are examined. Animal experiments designed to elucidate points of a fundamental character are briefly described. The indications for the use of esophageal leads are presented.

The Protective Effect of a Collateral Vascular Bed Upon Coronary Occlusion. Claude S. Beck, M.D., Cleveland, Ohio.

ABSTRACT

The epicardium was removed. The endothelial layer of the pericardium was roughened. The pericardium and pericardial fat became adherent. Bands of silver were placed around the major coronary arteries. These vessels were occluded, a little at a time, by successive operations. Almost the entire coronary tree was occluded with recovery of the dog. A capillary injection of myocardium was obtained through the collateral vascular bed thus established.

It would appear that the presence of a collateral vascular bed protects the heart from sudden occlusion of a major coronary artery. In this respect the operation will serve as a prophylaxis against the ravages of sudden coronary occlusion.

The Development of Mitral Stenosis in Young People With a Note on the Frequent Misinterpretation of a Middiastolic Murmur at the Cardiac Apex. E. F. Bland, M.D., Paul D. White, M.D., and T. D. Jones, M.D., Boston, Mass. See page 995.

Follow-up Study of Sixty-Four Patients With Right Bundle-Branch Conduction Defect. Francis Clark Wood, M.D., William A. Jeffers, M.D., and Charles C. Wolferth, M.D., Philadelphia, Pa. See page 1056.

The Effect of Irregular Cardiac Rhythms on the Minute Volume Output of Blood From the Heart in Human Beings. Harold J. Stewart, M.D., N. F. Crane, M.D., J. E. Dietrich, M.D., and W. P. Thompson, M.D., New York, N. Y.

ABSTRACT

Paroxysmal tachycardia, both when the auricles are beating regularly (supraventricular) and irregularly (auricular fibrillation), as well as the very slow cardiac rhythm of complete heart-block, may be associated with diminished minute volume output of blood from the heart in the resting individual. A fibrillating heart slowed by digitalis may be as effective a pump as is that same heart after reversion to normal rhythm, the heart still under the influence of digitalis.

The Normal Electrocardiogram in Two Hundred Individuals With Special Reference to the Chest Leads. William Hallaran, M.D., and R. A. Shipley, M.D., Cleveland, Ohio.

ABSTRACT

Electrocardiograms have been made on 100 men and 100 women between the ages of twenty and thirty-five years, all of whom had a negative history, negative cardiovascular examination, and normal blood pressure. The normal variations in duration, amplitude, and contour of the various complexes have been observed and recorded

in the three conventional leads and in a chest lead using the apex and left leg. Special attention has been paid to slurring of QRS and elevation or depression of S-T interval. In twenty-five cases the effect of varying the position of the precordial electrode, using this method of leading from the chest, has been studied. In forty cases, for comparison, the chest lead using the A-P position of the electrode has been employed. It has been found that: (1) the magnitude of the QRS and T-deflections in males falls within a higher range than in females; (2) there is no significant difference between the records obtained using as chest leads (a) the apex and the left leg and (b) the apex and the back; (3) variation in the position of the precordial electrode produces marked changes in the contour of the QRS complex but does not materially alter the T-wave.

The Clinical Value of the Fourth Lead, as Observed in 3000 Ambulatory Patients. Clayton J. Lundy, M.D., Lawrence L. McLellan, M.D., Charles M. Bacon, M.D., and Ray Merchant, M.D., Chicago, Ill.

ABSTRACT

Clinical and electrocardiographic data were studied in an attempt to determine the value of Lead IV. It was found that the fourth lead gave evidence which, either as confirmatory evidence or as an additional finding, was helpful in the diagnosis of all forms of heart disease. It added tangible proof of the presence of early rheumatic heart disease. In chronic arteriosclerotic heart disease the fourth lead was of independent diagnostic value in 20 per cent of the cases, and of confirmatory value in 40 per cent.

A Study of 150 Cases of Coronary Thrombosis Treated With Low Calorie Diets. Arthur M. Master, M.D., Harry L. Jaffe, M.D., and S. Dack, M.D., New York, N. Y.

ABSTRACT

In 150 cases of coronary thrombosis the treatment consisted of immediate and prolonged bed rest, an 800 calorie diet and morphine and codeine when necessary. The diminished food intake lowered the basal metabolism to minus 20 or minus 30, decreased the heart work, avoided gastrocardiac reflexes. It is believed that the low diet was responsible for the prompt disappearance of pain and for the favorable outcome of most of the cases. The mortality in the entire series was 13 per cent, in the case of first attacks, only 5.5 per cent. Sixty-seven and one-half per cent of the patients were able to return to work.

The following papers were read by title.

Observations on Cardiovascular Syphilis. Louis A. Kapp, M.D., New York, N. Y.

ABSTRACT

An analysis of a series of cases of cardiovascular syphilis is presented. The influence of various factors is discussed: (1) personal data (age, race, occupation, habits, etc.); (2) luetic infection (date of infection, Kahn or Wassermann reaction, other luetic manifestations, specific treatment); (3) other diseases or infections (hypertension, arteriosclerosis, focal infections, rheumatic fever, pulmonary tuberculosis, etc.).

The frequency, intensity, and onset of the outstanding signs and symptoms are stated. Laboratory findings are described. Subdivision is made into (a) simple aortitis, with or without widening of the aorta; (b) complicated aortitis with aortic insufficiency, hypertension, arteriosclerosis, etc., and (c) aortic aneurysm. Several unusual cases of aneurysm of the aorta—two with sudden death following

rupture of the aorta—are demonstrated. The effect of antiluetic therapy with special reference to cardiac insufficiency is discussed.

Acute Arterial Occlusion: Reestablishment of Adequate Circulation Through Collateral Arterial Pathways by Passive Vascular Exercises. L. G. Herrmann, M.D., Cincinnati, Ohio.

ABSTRACT

The author has utilized the principle of increasing the arterial circulation in an extremity by rhythmic changes in the environmental pressure. Eighteen patients with peripheral embolism or arterial thrombosis occurring as a complication of serious cardiovascular disease have been treated successfully by passive vascular exercises. A discussion of the pathological physiology of the peripheral circulation after sudden occlusion of a major artery is presented with evidence to show that this method offers a most efficient and practical means of overcoming, without strain or shock to the seriously ill cardiac patient, the circulatory disturbances which result from such sudden accidents.

The Etiology and Pathogenesis of Auriculoventricular Heart-Block: Report of Representative Cases With Detailed Histopathological Studies. Wallace M. Yater, M.D., Washington, D. C.

ABSTRACT

There appear to be three chief causes of this condition: calcification in the region of the A-V bundle, large gumma in the septum involving the bundle, and fibrotic interruption of the bundle or its branches. The first is usually the result of strain at the junction of the membranous and muscular portions of the septum or of calcification of the vegetations of subacute bacterial endocarditis. The third follows impairment of the vascularity of the conduction system. The blood supply of the conduction system is discussed. Representative cases are presented, with histological studies.

The Relationship of Heart-Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris, and Coronary Thrombosis. Jorge Salcedo-Salgar, M.D., Bogota, Colombia, and Paul D. White, M.D., Boston, Mass. See page 1067.

Paroxysmal Tachycardia. John P. Anderson, M.D., Cleveland, Ohio.

ABSTRACT

Conclusions are based on a study of 100 patients with paroxysmal tachycardia observed over varying periods up to twelve years. It is considered to be a functional heart condition carrying little or no danger to life but causing a great deal of misery to those so afflicted. The effects of various methods of vagal stimulation are discussed, as well as the effects of absorption from focal infections. Therapy by drugs such as digitalis, quinidine, sedatives, stimulants, gland extracts, ergotamine, and mecholin is presented.

Factors Influencing the Intensity of the First Heart Sound. Alexander Margolies, M.D., and Charles C. Wolferth, M.D., Philadelphia, Pa.

ABSTRACT

This study is an attempt to analyze the various factors which may influence the intensity of the first heart sound: namely, age, sex, thickness of the chest wall, blood pressure, heart rate, heart size, the presence of heart disease and certain other

diseases, the conduction time (P-R interval), and electrocardiographic evidence of myocardial damage and myocardial infarction. Five hundred patients with regular sinus rhythm, normal conduction time, and single first heart sounds were used. Sex was without influence. Hypertension, thyrotoxicosis, tachycardia, and small heart size tended to increase the intensity. Increased age, bradycardia, apical systolic murmurs, cardiac enlargement and myocardial disease tended to diminish the intensity. The most influential single factor was the auriculoventricular conduction time as measured by the P-R interval. When the P-R interval was short (0.12 to 0.14 second), the sound tended to be loud; when the interval was long (0.18 to 0.21 second), the sound tended to be weak; intermediate P-R intervals (0.15 to 0.17 second) tended to be associated with sounds of medium intensity. Furthermore, the evidence suggested that most of the other factors were chiefly operative through their influence on the conduction time. The three exceptions were myocardial infarction and thickness of the chest wall which tended to diminish the intensity and mitral stenosis which increased it.

Electrocardiograms on 167 Healthy Infants and Children. Clough Turrill Burnett, M.D., and Evelyn Laura Taylor, A.B., Denver, Colo. To be published in AM. HEART J.

The Orthodiagram in the Diagnosis and Treatment of Heart Disease. Chester M. Kurtz, M.D., Madison, Wis.

ABSTRACT

By the method of Eyster and Hodges 2,000 orthodiagrams have been made in 1,350 cases. An extensive follow-up study has been carried out with the same technic. Certain conclusions are drawn as to characteristic change in the shape of the heart in the presence of various valve lesions. It is also shown that by using the prediction formulas of Eyster and Hodges, the normal range is extremely narrow and relatively small degrees of enlargement can be detected with fair accuracy. The importance of certain physical signs in determining cardiac enlargement is demonstrated.

The Effect of Ouabain Upon Electrocardiograms of Specific Muscle Lesions. J. S. Robb, M.D., M. S. Dooley, M.D., J. G. F. Hiss, M.D., and R. C. Robb, M.D., Syracuse, N. Y. See page 1012.

Massive Left Auricle. Louis Faugeres Bishop, Jr., M.D., and Andrew Babey, M.D., New York, N. Y.

ABSTRACT

The clinical features of two cases are reported and the differential diagnosis from effusions and tumors of the chest and esophagus is discussed.

DISCUSSION

Discussion of the paper, "The Results of Treatment of Cardiovascular Syphilis," by Drs. Padget and Moore.

Dr. Edwin P. Maynard, Jr., Brooklyn, N. Y.—I should like to ask Dr. Padget from what point he calculated life in those patients who had inadequate and adequate treatment. Did he take the duration of life from the time they began treatment or from the time of infection with syphilis? It is an important point in statistical analysis to date the duration of life from some definite point in the course of the disease rather than from the time the patient happens to come in contact with the doctor.

Dr. Homer F. Swift, New York, N. Y.—Was there a distinct difference in the relative comfort of these two groups of patients? Were the symptoms and signs of the well-treated patients less than those in the poorly treated group?

Dr. Julien Benjamin, Cincinnati, Ohio.—Will Dr. Padget please tell us what he considers adequate treatment; and whether he is considering as adequate treatment that received during the course of cardiovascular syphilis, or that received early in the course of the disease?

Dr. Joseph E. Hirsh, Birmingham, Ala.—Dr. Padget makes no differentiation between those patients who come in compensated and those who are decompensated on admission. My experience in the South, where we have a great number of negroes with cardiovascular syphilis, is that if the patients are compensated, antiluetic treatment may help them; if they are decompensated with dyspnea, edema, and all the classical signs of heart failure, there is no improvement. Once an individual with syphilitic heart disease becomes decompensated, he remains decompensated, despite all specific treatment, whether it be arsenic, iodides, bismuth, or mercury. We find that in such patients the mortality is practically 100 per cent, despite all treatment.

Dr. Roy W. Scott, Cleveland, Ohio.—Some ten years ago I became interested in this subject but did not follow it through, so far as therapy is concerned, as adequately as Dr. Moore has since done. We were very much impressed, and so stated at the time, that once the intervention of circulatory failure in the course of syphilitic aortic insufficiency occurred, no treatment that we were able to supply made any difference in the clinical course of the disease.

Dr. M. A. Mortensen, Battle Creek, Mich.—I should like to ask if any of these patients had antiluetic treatment prior to the discovery of cardiovascular lues. Many patients know that they have had syphilis for years and have had more or less treatment prior to the diagnosis of cardiovascular syphilis. In these cases may not the final picture be due to inadequate treatment?

Dr. Paul Padget, Baltimore, Md.—I am grateful to Dr. Maynard for bringing up the question concerning dating the duration of life. The duration of life in these patients was dated from the onset of symptoms definitely referable to the cardiovascular system, with the exception of those who, in the course of routine investigation, were found to have cardiovascular syphilis. Obviously this introduces some uncertainties, but in this series we saw no better way to meet the problem. To answer Dr. Swift, we shall later go into considerable detail concerning the ability of these patients to work. Briefly, alleviation of symptoms was a very conspicuous feature in those who were well treated and many regained ability to work. In answer to several questions about the amount of treatment—we consider adequate treatment in the presence of cardiovascular syphilis to be at least one year of continuous treatment with heavy metal and arsenicals in which the heavy metal phase in emphasized, as outlined by Moore, Danglade, and Reisinger. The minimum of the "adequate treatment" group of this series was less than that, but there were only three patients so classified who fell short of approximating what we considered to be the true minimum, i.e., a year of treatment. In regard to treatment for early syphilis, it is to be emphasized that no patient in this group had had adequate treatment for early syphilis, and only a few had had any treatment at all prior to the discovery of the cardiovascular lesions. The incidence of cardiac failure was the same in the "inadequate treatment" and "adequate treatment" groups (approximately one-fourth of each) but was higher in those who died in less than a year of observation.

Discussion of papers, "The Significance of the Electrocardiographic Changes in Diphtheria" and "The Pathological Analysis of Diphtheritic Myocarditis With Especial Reference to Electrocardiographic Findings," by Drs. Smith, Burkhardt, and Eggleston.

Dr. Arthur M. Master, New York, N. Y.—I think it is not surprising that one often fails to find pathological changes at post-mortem examination, for we know that there may be functional as well as anatomical changes in the heart muscle. In certain individuals auriculoventricular conduction defects may appear if the heart rate is speeded up by exercise or by giving amyl nitrite, but as soon as the stimulus is over, the electrocardiogram returns to normal.

Dr. Clarence E. de la Chapelle, New York, N. Y.—I should like to ask Dr. Smith whether in those hearts which had either auricular or ventricular thrombosis he found underlying changes in either the endocardium or the myocardium; also, whether in the cases that showed diffuse fibrosis, he saw any evidence of activity, either in a healing state or still fairly active.

Dr. Hugo Freund, Detroit, Mich.—I should like to ask Dr. Smith if there were any changes in the intracardiac ganglia.

Dr. W. Bernard Kinlaw, Rocky Mount, N. C.—I should like to ask if any of the patients have developed true definite block and recovered.

Dr. E. A. Burkhardt, New York, N. Y.—In the seventeen cases showing conduction changes, eleven developed an auriculoventricular block. This complication was invariably fatal. Some patients with intraventricular block did recover.

Dr. Lawrence Smith, New York, N. Y.—We have not been able to demonstrate any changes in the ganglion cells. Those studies we tried to carry out systematically, but our results have not been uniform. Apparently the lesion is one of the contractile tissue, rather than of the nerve cells proper. As far as the endocardial lesion is concerned, Dr. de la Chapelle, the changes have been minimal with one or two notable exceptions. There seems to be nothing active beyond these fibrotic sclerotic changes.

Discussion of the paper, "Peripheral Venous Phenomena in Congestive Heart Failure," by Dr. Kerr.

Dr. Jacob Polevski, Newark, N. J.—In connection with pulsation of the veins of the neck, I have seen two cases of young children with mitral stenosis in a perfect state of compensation with no evidence of pronounced right cardiac dilatation and surely no relative tricuspid insufficiency, in which the upward pulsation in the jugulars led to a diagnosis of patent foramen ovale. One of these patients subsequently died from pneumonia, and the autopsy findings confirmed the original cardiac diagnosis.

Dr. Harold E. B. Pardee, New York, N. Y.—Dr. Kerr has spoken of venous pulsations as associated particularly with right heart failure. He has also, however, mentioned the venous pulsation in association with tricuspid stenosis. I wish particularly to emphasize this latter fact because I have also noticed that there was a marked auricular venous pulsation in the veins of the neck in patients whom I have considered to have tricuspid stenosis. Two of these patients did not show any particular degree of heart failure, and in one of these the pulsation of the veins of the neck was the chief complaint for which the patient applied for treatment. This, I think, is an important diagnostic sign of tricuspid stenosis. It should be especially emphasized because in the diagnosis of this valve lesion we are in need of diagnostic signs. The similarity of the murmur to that of mitral stenosis and the frequent

presence of both lesions present a considerable problem in diagnosis. Because of the difficulty in this diagnosis I feel that I should mention another diagnostic sign which has been found in patients with tricuspid stenosis even though it is somewhat off Dr. Kerr's subject. This is the finding of a very sharply peaked auricular wave, like a high gable roof, and well over 2 mm. in height.

Dr. Simon Dack, New York, N. Y.—I should like to ask Dr. Kerr if he has been able to differentiate between functional tricuspid insufficiency and that due to organic changes in the tricuspid valve with the aid of polygraphic records. In one patient studied at Mount Sinai Hospital, on whom a post-mortem examination was made, there was a definite organic tricuspid stenosis and yet the polygraphic record was not characteristic of that condition.

Dr. William J. Kerr, San Francisco, Calif.—I would agree with Dr. Master that patent ductus arteriosus would be one of the conditions in which systolic pulsations transmitted along the venous system would be observed. With respect to functional and organic conditions of the tricuspid valve, I should like to say that we do not think, on the basis of the mechanism concerned here, that it makes a great deal of difference whether one is dealing with a relative or so-called functional tricuspid insufficiency or with one which is organic. The relative insufficiencies, of course, are usually much more transient, but in practically every patient with congestive failure based on failure of the right heart, no matter what the cause, these pulsations will be present. In patients with an organic condition of long standing, the waves may be more marked, but this is only a matter of degree. We have made use of the double wave auricular and ventricular pulsations in the diagnosis of tricuspid stenosis, and I think that that is important, as Dr. Pardee brought out.

Discussion of the paper, "The Relationship of Blood Pressure, Peripheral Vasomotor Activity, and Environmental Temperature," by Dr. Oughterson.

Dr. James P. O'Hare, Boston, Mass.—May I ask if all emotional factors were eradicated? Are there emotional factors produced in temperament, environment, etc.?

Dr. Louis F. Bishop, Jr., New York, N. Y.—Were these blood pressures recorded by any method of recording machine or were they taken with the ordinary mercurial instruments?

Dr. Ashley W. Oughterson, New Haven, Conn.—In regard to Dr. O'Hare's question, all that I can say is that as you talk to these patients, they do not mind the temperatures to which they are exposed. However, a rapid shift of 30 to 35° F. involves some little discomfort. If, for example, patients are in a state of full vasodilatation at a room temperature of 85° to 87° F., and superimpose on that an emotional factor, you may get an immediate vasoconstriction. However, the changes initiated by emotional factors do not last over long periods. Nevertheless I should hesitate to say that an emotional factor does not play some part. As regards the blood pressure, we have no automatic device. We have tried to make many but we have not succeeded. The blood pressures are usually taken at fifteen-minute intervals; some are taken at ten-minute intervals. The temperatures are recorded continuously.

Discussion of the paper, "The Influence of the Heat Regulatory Mechanism on Raynaud's Disease," by Dr. Pearse.

Dr. Irving S. Wright, New York, N. Y.—I was very much interested in this paper. There is one problem which I should like to bring to Dr. Pearse's attention. During the past several years, we have seen an occasional patient suffering from atypical Raynaud's syndrome in whom it has been impossible for us to induce

It is worth a moment's time to restate the problem. We have accepted, since the time of Raynaud, that Raynaud's disease is a vasomotor disorder attributable to some hypersensitivity or overactivity of the sympathetic mechanism. Sir Thomas Lewis threw a sceptical note into the assembled opinion concerning this respected tradition. He found that some patients with Raynaud's disease reacted to local stimuli following interruption of the sympathetic pathways. He postulated some fault of the peripheral vessels as the primary factor in this disease. This observation immediately started us thinking. As a result, many new, interesting facts are developing.

Now it is unquestionably true that if lumbar sympathetic ganglionectomy is performed in cases of Raynaud's disease, vasoconstrictor color reactions are never effected by cold or lowered environmental temperature. Following removal of cervical and upper thoracic ganglia, with complete removal of the vasomotor fibers to the hands, there is a certain number of cases in which cold produces ischemic color reactions. There is also a group of cases in which these reactions are abolished. It is the former group that requires further explanation. The work of Dr. White and Dr. Freeman may furnish the answer. They have shown that the sympathectomized vessel becomes hypersensitive to epinephrine and that color and temperature responses remaining after operation can be produced by stimuli causing an outflow of epinephrine. Why the upper and lower extremities behave differently remains an enigma.

As I said before, this problem may not be of broad, clinical interest at the moment. Future work along these lines may be applicable to the questions of hypertension and of many clinical phenomena that involve reactivity of the blood vessels.

Dr. Herman E. Pearse, Rochester, N. Y.—To take the questions in chronological order, that of Dr. Wright concerning cases in which there is no response to cold is first. In this reaction let me warn of the phenomenon of overcooling of which Dr. Kerr is so well aware. If the extremities are cooled below about 13° C., there is then the reaction of dilatation rather than constriction. So, in testing with cold, one has to be careful not to overcool the extremity below this critical temperature. However, it is observed that an occasional patient will not respond to an appropriate degree of cold under test conditions. I have observed the paradoxical reaction to heat but have not studied any such patients. I am very much interested in Dr. Oughterson's comment about the gain in weight, because there is a linkage between the psychic personality and the general bodily state of these individuals who have exaggerated phenomena, just as there is a linkage with body type in gall-bladder disease, in duodenal ulcer, in Graves' disease, and so on. And it is true that one means of amelioration of symptoms is to have the patients gain weight. I have found it rather difficult to accomplish this because they are kinetic individuals and do not gain weight easily. Finally, I am very much indebted to Dr. Kerr for his suggestion of the achlorhydria, and he may be assured that I will investigate it. One must consider many factors in these individuals since it is my feeling that, though we use the term "Raynaud's disease," perhaps it is not a disease entity but a symptom-complex in which there are diverse motivating factors.

Discussion of the paper, "Observations Upon Electrocardiographic Tracings Obtained by the Use of Esophageal Leads in the Human Subject," by Dr. Brown.

Dr. Arthur M. Master, New York, N. Y.—Very many interesting facts have been brought out. On the other hand, there is a little difficulty in using the esophageal lead. I wonder if Dr. Brown has made comparisons with graphs obtained by chest leads, particularly when one electrode is placed on the back at the level of the third, fourth, or fifth dorsal vertebra. Chest leads are very easy to use whereas the esophageal lead may be difficult.

around the ward helping as a ward orderly. The pain and discomfort which he had in the chest are gone completely, even on moderate exertion. We have not tried him out on any extreme exertion, but work as a ward orderly caused no distress. From the clinical point of view, I should say that the results were highly satisfactory at the end of four months. Certainly, subjectively he is tremendously improved, and objectively the operation did no harm.

A second patient, a fifty-three-year-old man, came from a family with a history of coronary disease. Two brothers had died and a sister had met sudden death. This man, a salesman, finally had to give up his work over a period of three years because of pain on the slightest exertion. Like the first patient, he had no evidence of failure. The circulation time was within normal limits, the metabolism was normal, and there was no evidence of disease of the gastrointestinal tract that could in any way explain the symptomatology. He withstood the operation very well. At the end of five days, he suddenly developed evidence of occlusion of the aorta at its bifurcation and died within twelve hours. At post-mortem examination, it was found that he had excellent adhesions as the result of the operative procedure, and he had a large thrombus at the bifurcation of the abdominal aorta over an atheromatous area. We cannot say very much about the results in this second case, except, first, he withstood the operation very well, and apparently was recovering; and, second, the adhesions produced operatively were well on their way to formation.

The third patient was a fifty-one-year-old executive with a typical history of angina of effort of seven years' duration. Usual medical therapy gave only palliative relief. Finally, two years ago, he was forced to give up all activities. One year ago he had a total thyroidectomy. This procedure was followed by relief from pain, but, when an effort was made to relieve him of his myxedema, pain reappeared. After one year's futile effort to establish a favorable dose of thyroid he was operated on by Dr. Beck. He withstood the operation very well and has made an uneventful recovery. Now, six weeks later, he has had no recurrence of pain, although the dose of thyroid which produced pain preoperatively is being administered. Also activities about the hospital, which brought on pain before operation, are tolerated.

A fourth patient, a surgeon aged fifty years, with definite subjective and objective evidence of angina, was operated on. This man, suffering for five years, refractory to medical therapy, finally became totally disabled about three and a half years ago. He gave a history suggesting coronary thrombosis two and one-half years ago. There was no evidence of congestive failure, and the circulation time was within normal limits. His convalescence from the operation was uneventful, and now, five weeks later, he is comfortable and has but rare mild anginal attacks.

In summary, four patients with severe coronary sclerosis with incapacitating angina have been operated on with operative recovery in all cases. One patient died five days later from an aortic thrombosis at the bifurcation of the abdominal aorta. The other patients at this early date have all shown striking improvement, and it is hoped that the new coronary circulation will be of lasting aid to the heart.

Dr. E. Cowles Andrus, Baltimore, Md.—It seems to me Dr. Beck is to be congratulated upon the careful, philosophical fashion in which he approached the problem. The possibility of developing a collateral circulatory bed in the heart is, of course, of fundamental importance. There are one or two questions I would like to ask. It is too much, of course, to demand that the exact conditions which the need for such an operation would imply be reproduced in experiments. But in coronary occlusion or in gradual diminution of the coronary flow in individuals with coronary sclerosis over a period of years, there is a time element which is difficult to meet, I suppose, in the acute experiment. Specifically, I personally should like to know the lapse of time between the implantation of this graft or the procedure itself

calculated to develop a collateral circulation and the ligation of these arteries. Is it possible to get the graft to take *ex post facto,* so to speak?

The problem represented by acute coronary occlusion leaves the heart with an infarction upon which collateral circulation must be developed. The problem, as I understand it, as presented by Dr. Beck, is, first, the development of collateral circulation and later the superimposition of a reduced coronary blood supply.

I should like to mention a few experiments by no means so complete as those of Dr. Beck's, which Dr. Rienhoff has been undertaking in Baltimore and with which I have been associated—the implantation of the omentum through the central tendon of the diaphragm about the heart. We can only say that judged by the effect of ligating the major arteries, a collateral circulation has developed. We have no injection preparations as yet. In stripping the graft from the heart, it appears that the blood supply has passed from the graft into the myocardial tissue.

Dr. George Fahr, Minneapolis, Minn.—In evaluating this or any other procedure for the establishment of a collateral circulation in the heart, it is necessary to know how long it takes to establish this adequate collateral circulation. I am therefore asking Dr. Beck to inform us how long it takes to establish this collateral circulation from the outside. I am asking this because G. von Anrep, who has done a number of these experiments on dogs, assures me that it takes over a year to establish an adequate circulation.

Dr. Louis Gross, New York, N. Y.—It would be of interest to learn whether Dr. Beck has attempted to ascertain the changes which may take place in the blood vessels of the dog's pericardium following gradual occlusion of the coronary vessels without previous epicardiectomy. In the human being, I have been able to show that if coronary sclerosis and occlusion take place slowly, there occurs quite a considerable development of epicardial vessels. I have also shown that intramyocardial anastomoses become increasingly prominent with advancing age. Apparently this is a normal physiological process and takes place slowly. With this in mind, Dr. Lester Blum and I became interested in the question of experimentally increasing these intramyocardial collateral vessels at a rate considerably faster than that which apparently occurs in the human heart. For reasons which I have not time to go into, we finally decided that a reasonable approach would be to tie off the coronary sinus in dogs. This was performed in a large number of dogs with extremely interesting results. Almost immediately following the coronary sinus tie-off, the coronary artery tree becomes enormously increased in extent. This can be determined easily by injection studies.

We then subjected these dogs to the crucial experiment of sudden occlusion of the most important coronary branch—the left anterior descending. In these experiments we were careful to tie off the vessel and cut it between ligatures. As is well known, such ligation of the left anterior descending coronary branch performed in the intact animal produces a large infarct almost invariably. However, when we performed this operation on a number of dogs which had been previously subjected to coronary sinus tie-off, either the infarct was completely missing, or, in fewer instances, the infarct which resulted was considerably smaller than is generally found in unprepared animals. In other words, coronary sinus tie-off in the dog's heart so completely transforms the coronary artery tree that it is either impossible or very difficult to produce an infarct in the heart so treated even by employing one of the most severe and dramatic methods at our disposal (sudden occlusion of the left anterior descending coronary branch).

It seems, therefore, that by some such means, at least in the dog's heart, one is able so to affect the myocardial vessels as to stimulate the development of a compensatory vascular tree which apparently can function under extremely adverse

circumstances. It is of interest that in the dog the operation takes a maximum of twenty minutes to perform, requires no splitting of the ribs, and leaves the pericardium relatively intact.

Dr. C. W. Greene, Columbia, Mo.—I have watched the development of the announced results of Dr. Beck with great interest. It seems to me a plausible and hopeful method of producing some slight improvement in a damaged coronary circulation. The point I raise, however, is that the data from the experiments on the injection of methylene blue seem to me to indicate rather a good collateral circulation of the anastomotic type, a relation that we have learned in recent years to be present in the dog's heart. I am slow to accept the view that the collateral circulation is stimulated by the technic of coronary obstruction used in this new operation. It is perfectly understandable why Dr. Beck should proceed from the standpoint of clinical condition of occlusion and try to imitate it; but from the standpoint of facilitating the development of an anastomosis, it does not seem necessary to occlude the coronary artery experimentally. I am wondering, therefore, Dr. Beck, if you cannot reverse the interpretation and method with greater hope of quickening the development of an anastomotic system by leaving the coronary circulation unobstructed.

Dr. Claude S. Beck, Cleveland, Ohio.—In answer to Dr. Andrus' question, I might say that when a portion of the myocardium is destroyed by infarction the damage is irreparable. The scar produced by an infarct does not possess the property of contractility. The blood supply to such scars is not nearly so essential as is the blood supply to functioning muscle. The operation that I am developing will give the best results in those cases in which fibrosis of the myocardium is not far advanced. Obviously, little can be expected from the heart when myocardium has been replaced by scar and fat. I believe the operation can prevent further replacement changes in myocardium.

The experiments that were illustrated by colored lantern slides were carried out in this rotation: The epicardium was stripped off the heart at the first operation and adjacent tissues were sutured to the myocardium. For the collateral bed we used fibrous pericardium, pericardial fat, pedicle grafts of skeletal muscle from the chest wall and omentum brought up through an opening in the diaphragm. Usually at the same operation we placed silver bands around the right coronary artery, the descending ramus of the left, and the circumflex ramus of the left coronary artery, and these silver bands were slightly compressed so that partial occlusion was produced. The second operation was carried out after an interval of several months. At the second operation one of these major arteries was completely occluded. We found by experience that we could occlude the descending ramus of the left or the circumflex ramus of the left coronary artery or the right coronary artery as a routine without fatality if the occlusion was carried out in two stages. Further occlusion was done in subsequent operations.

The earliest evidence of anastomosis between extracardiac and cardiac vascular beds was after two to three weeks. In one experiment we could demonstrate dye in the myocardium two weeks after the collateral vascular bed was produced. The dye was injected through the extracardiac vascular bed. In another experiment anastomoses were observed three weeks after operation. The anastomoses grow larger as time elapses. I hesitate to make the direct application of these observations in animals to the human patients upon whom I carried out my operation. Our three patients stated that they felt the beneficial effect of the operation as early as three or four weeks after the collateral bed was attached to the heart.

The evidence presented by Dr. Gross is extremely interesting to me. Perhaps in the future it may have some clinical application. At the recent meeting of the

American Surgical Association I presented some of our work, and the question was asked me by several surgeons what happens if you ligate the vein along with the artery. During the war Sir George Makins advocated ligation of the corresponding vein when an artery had to be ligated. He has shown that the incidence of ischemic necrosis in an extremity is reduced by ligation of the vein. Dr. Gross has shown that this principle can be applied also to the heart. Venous ligation increases the peripheral resistance and would tend to keep the blood in the capillary bed of the heart. It may be of value in distributing the blood to various parts of the myocardium, but I do not see how occlusion of the vein can bring additional blood through the stenosed coronary arteries to the heart. Our experiments have pointed out the importance of distribution of blood to various parts of the myocardium. A relatively small area of myocardium made ischemic will bring the heart to a standstill. The experiments illustrate the significance of localized ischemia in contrast to generalized ischemia of the myocardium. I believe Dr. Gross' results can be explained on the basis of an improved distribution of blood to various parts of the myocardium rather than on the basis of an augmented arterial flow.

I do not know whether I got Dr. Greene's question. It is a fact well established by surgeons that partial occlusion of an artery is followed by the development of a compensatory circulation.

I would like to make these concluding remarks: I believe we have produced a new blood supply to the heart by operation. I do not believe our experience is sufficient to say that we have corroborated the experimental facts on patients suffering from sclerosis of the coronary arteries. Until this has been accomplished, the operation should be regarded as an experimental procedure. The operation is not without hazard and I hope surgeons will not accept the procedure until it has been satisfactorily applied.

Addendum: During the interval of several months since this presentation was made I operated upon several patients with coronary sclerosis. The beneficial results of the operation are exceeding my expectations. The degree of improvement following operation is most gratifying. It seems to me now that a new field of surgery has been opened up.

Discussion of the paper, "A Follow-Up Study of Sixty-Four Patients With Right Bundle-Branch Conduction Defect," by Drs. Wood, Jeffers and Wolferth.

Dr. Arthur M. Master, New York, N. Y.—I had occasion this morning to mention some cases of normal people who, when the rate was increased by drugs or exercise, developed intraventricular block, and, as the rate slowed down, the electrocardiogram became normal. Perhaps they fall into this class. Physicians who have been interested in electrocardiography have known that there was a type of intraventricular block as described in which the prognosis was good. I think there have been a few publications to this effect but in no case in detail or in a follow-up study. I think that Drs. Oppenheimer and Mann reported this before the Society of Experimental Biology and Medicine, and they called this the S-wave type of intraventricular block because the notching and the slurring and the widening are in the second half of the QRS group. It seems to me that in just this point emphasis must be made. An electrocardiogram that shows the ordinary type of bundle-branch block is, I think, of great significance, but if the widening and notching and slurring are in the second half of the QRS complex the patient's prognosis is much better.

Dr. Samuel S. Levine, Boston, Mass.—This paper, I think, calls attention to the fact that there is room for ordinary medical sense in sizing up cardiac problems. The electrocardiograph tests certain things. When it does not altogether fit in with what you perceive by other judgment, it is worth while to look with sus-

picion on the interpretation of the cardiogram. A contribution like this adds emphasis to just what we mean by clinical sense. We are attaching too much importance in a prognostic sense to the cardiogram. Diagnostically, we have been helped a great deal. It is very curious that the prognosis in patients with angina pectoris, which I reviewed a few years ago, was better in those patients with definite angina pectoris and abnormal electrocardiograms than it was in those with normal electrocardiograms. A follow-up study of 100 patients with angina pectoris revealed that those who had wide QRS complexes or bundle-branch block lived longer than those patients with angina pectoris who had essentially normal curves. So from the prognostic point of view we are not on such very firm ground. Diagnostically, I am aware that electrocardiography has been helpful. Ordinary clinical sense is still an important factor in judging prognosis, and it is difficult enough at the best.

Dr. Meyer Sclar, Brooklyn, N. Y.—I had a patient come to me in 1933. He brought with him an electrocardiogram taken in 1922, which showed a marked right bundle-branch block. When I saw him in 1933, I was surprised; I was under the impression he should have been dead by that time. All he complained of was some vague precordial discomfort, and he was able to carry on his usual routine as an insurance man. I immediately communicated with a number of the leading cardiologists in the country and received several replies, among others from Dr. B. S. Oppenheimer, of New York, and Dr. Paul D. White, of Boston, and each informed me that he had had quite a number of patients of right bundle-branch block, and that they had all carried on fairly comfortably, actively, and usefully. I am glad that Dr. Wood and Dr. Wolferth throw a good deal of optimism upon the right bundle-branch block.

Dr. Wallace M. Yater, Washington, D. C.—These observations fit in very well with the fact that on careful sectioning of the conduction system of the heart one may find in a surprising number of cases extensive and very severe lesions of the bundle branches without apparent involvement of the myocardium, and it is quite possible that these changes have existed for years. It would seem that the conduction system is the first part of the heart to feel a diminution in blood supply. It is interesting to note also that these patients may show various types of conduction disturbances without myocardial insufficiency. As I said last year at the American Heart Association meeting, we are making too many electrocardiographic diagnoses without a basis in anatomical fact. If some of us would get busier and do this type of very tedious work, I am sure we should find that these changes exist much more frequently than we have thought.

Dr. J. H. Crawford, Brooklyn, N. Y.—About four years ago I saw a young woman who had been rejected as a school-teacher on account of a slight murmur in the region of the third and fourth left interspaces close to the sternum. She had an electrocardiogram exactly the same as Dr. Wood has described. She had been a champion in many different types of athletics which must have thrown considerable strain on the heart, but she had no symptoms whatsoever. There was no cardiac enlargement and nothing to indicate that there was anything wrong with the cardiovascular system. Since then her activities have been unrestricted, and she has had absolutely no symptoms. It is the same type of case as those which Dr. Wood has just described.

Dr. Harold E. B. Pardee, New York, N. Y.—Dr. Wood has certainly impressed us with the idea that this type of bundle-branch block is associated with a better prognosis than the other type. I do not think, however, that he wished to impress us with the idea that it must have a good prognosis, nor do I think he wished to impress us with the idea that the other type must have a bad prognosis. I am

quite sure than everyone who sees many electrocardiograms will find that he has seen a number of curves of the other type in persons who are just as free from symptoms of cardiac failure as those which have attracted attention here. I would like to know what Dr. Wood's experience has been in this regard. I feel also that, when one talks about prognosis in electrocardiographic features, it is very much like talking about prognosis in mitral stenosis or more like talking about the prognosis of a certain type of heart murmur. It does not seem to me to be a logical thing to do. There has been a great deal of that sort of talk, and I feel that it is all wrong. Prognosis must depend upon the patient who has heart disease, not upon any isolated finding which he may have. If there is only one finding, it is well to put that into the picture, but that is not the whole picture; the patient is the whole picture.

Dr. John Wyckoff, New York, N. Y.—In the Cardiac Clinic in which I have worked, we have had a rule that no diagnosis or prognosis must ever be made on a single symptom or a single physical sign. It seems to me that this paper and Dr. Levine's and Dr. Pardee's discussion of it show that that rule is a fairly safe one to follow.

Dr. Francis Clark Wood, Philadelphia, Pa.—The question was raised as to whether any of these patients had temporary bundle-branch block and therefore were in better condition than if they had had permanent block. Three of the sixty-four patients showed temporary returns to normal intraventricular conduction from time to time. The rest probably had permanent conduction defects since none of their tracings showed normal QRS complexes.

Discussion of the paper, "The Effect of Irregular Cardiac Rhythms on the Minute Volume Output of Blood from the Heart in Human Beings," by Drs. Stewart, Crane, Dietrich, and Thompson, New York, N. Y.

Dr. Samuel S. Levine, Boston, Mass.—I am not clear whether Dr. Stewart wants us to believe that it is well for the heart to work hard. The question is: Is it better for that heart to be doing more work? If at the end of the experiment the heart has been restored to a normal rhythm and the amount of foot pounds or work the heart has done has increased, it sounds as if it is a good thing, but it is not necessarily so. The opposite of that is what we are trying to do in resting the heart. If improvement takes place from thyroidectomy, it takes place because the work of the heart is diminished, not because it is increased.

I am putting this in the form of a philosophical question. It would certainly seem as if fibrillators are better off in many instances when the heart is regular, but I do not know that the theoretical evidence that the heart is doing more work is adequate proof that it is better for that heart. I can readily conceive of the fact that the heart is better off eventually, over years, if it is doing less rather than more work.

Dr. Harold J. Stewart, New York, N. Y.—For a given size of the heart at rest, a certain amount of work should be performed. That falls in line, of course, with Starling's law of the heart. Now it has been found, according to Starr and his associates' work, that when the size of the heart is so large that the work which that large heart performs is not commensurate with the size of that heart, those patients either suffer from heart failure or are threatened with heart failure.

Discussion of the paper, "The Clinical Value of the Fourth Lead, as Observed in 3000 Ambulatory Patients," by Drs. Lundy, McLellan, Bacon, and Merchant.

Dr. Arthur M. Master, New York, N. Y.—I recently reported fourth leads in normal individuals. I think that more harm than good was done because I would

report that in normal persons the Q-wave, for example, in the fourth lead is at least two millimeters in size. Hence many think that, if a Q-wave is of one millimeter in size, the patient has an abnormal heart. I think it brings up the point that Dr. Levine and Dr. Pardee brought out, but perhaps a little differently. I think the electrocardiogram and the electrocardiograph are all right, but I think the difficulty lies in interpretation. You have to know the normal electrocardiogram, and you must use a knowledge of clinical medicine in the interpretation. Here are some more interesting things that we learned about the fourth lead. We found, first of all, that you do not need the fourth lead except in few cases. If you have an entirely normal three-lead electrocardiogram but feel clinically there is heart disease, then take a fourth lead. We found the only thing that could be depended upon in the fourth lead was the upright T-wave. If the T-wave is upright, we feel that is abnormal. On the other hand, here again if you take electrocardiograms in children with an electrode anywhere between the sternum and the apex or beyond, you find upright T-waves in more than 60 per cent of the cases. There have been publications on the value of a fourth lead in rheumatic heart disease, and the diagnosis has been made on a T-wave that is upright in the fourth lead, whereas we know that in young children this upright T-wave is a normal finding. I should like to describe the way I feel about the fourth lead by bringing up the case of a patient with a dropped heart. Now a patient with a long narrow heart often has a right ventricular preponderance on the electrocardiogram; he often has a large auricular wave and often has a blowing systolic murmur at the apex, and yet we know he has not any heart disease. Those three phenomena are associated with his dropped heart. In a similar manner you must use your clinical judgment when drawing conclusions from the electrocardiogram.

Dr. Simon Frucht, Brooklyn, N. Y.—Soon after Wolferth and Wood published their article on Lead IV with reference to coronary thrombosis, I began a study of Lead IV in other conditions. I found that a deepened Q_4 was present in practically very case of mitral stenosis. In hypertensive heart disease Q_4 was absent.

The reader of the paper presented an electrocardiogram of a young child which showed a right axis deviation and a deep Q_4. As the child grows older, the position of the heart changes, and the electrocardiogram assumes a more normal form. The form of QRS in Lead IV varies according to the position of the heart and the state of the myocardium. Rotation of the heart to the right or left causes Q_4 to increase or decrease in amplitude. Pronounced mitral stenosis, in which the heart enlarges to the right and rotates to the left, shifting the apex backward, gives rise to a deepened Q_4 together with a right axis deviation. Long-standing hypertensive heart disease, in which the heart enlarges to the left and rotates to the right, bringing the apex forward, gives rise to an absent Q_4 in conjunction with a left axis deviation. Lead IV visualizes anterior and posterior axis deviations.

Dr. Charles C. Wolferth, Philadelphia, Pa.—It is many years since Einthoven and his successors began to work on the standardization of limb leads of the electrocardiogram; nevertheless, it has been shown today that their work has not been completed.

In the attempt to standardize the so-called fourth lead, we are faced with a complexity that does not obtain in the study of the three limb leads, namely, the position of application of electrodes. This subject has been referred to this afternoon. Everyone who has looked at hearts under the fluoroscope knows that from patient to patient the position of the apex varies tremendously. We have concerned ourselves with this problem of standardization of chest leads for four years. My colleagues, Drs. Wood and Edeiken, have come to the conclusion that it is important to determine the position of the apex by fluoroscopy so that its relation to the

position of the anterior electrode is known. This precaution is not often necessary in clinical work since the position of the apex can usually be located with reasonable accuracy by palpation.

If the admittedly rough standards now available are adhered to, chest leads have diagnostic value in addition to their usefulness for the demonstration of acute or old myocardial infarction. Thus, in a certain proportion of patients with angina pectoris, one gets T-wave changes such as are not encountered in normal controls, provided that the electrode is accurately applied over the apex. Upright T-waves in Lead IV, under these circumstances, have significance comparable to that of inverted T-waves in Leads I and II. Furthermore, when the electrodes are accurately applied, the absence of an initial downward deflection also has considerable significance. However, neither of these abnormalities as an isolated finding warrants the diagnosis of myocardial infarction. It is of interest, however, that the combination furnishes an almost certain indication of anterior infarction.

Dr. Clayton J. Lundy, Chicago, Ill.—I can add that this paper attempted to show the electrocardiographic findings in clinically diagnosed cases. We did not make the diagnoses upon the basis of the electrocardiographic findings.

Discussion of the paper, "A Study of 150 Cases of Coronary Thrombosis Treated With Low Caloric Diets," by Drs. Master, Jaffe, and Dack, New York, N. Y.

Dr. Jacob Polevski, Newark, N. J.—Mr. Chairman, about a year ago at the annual meeting of the American Therapeutic Society,* I reported a diet that I instituted at our hospital several years ago. I called attention to the fact that by reducing the weight of the patient we are very often able to approach an equilibrium between the heart's ability to supply and the tissue's demand.

This diet consists of a five-day subsistence on fruit and vegetables with the exclusion of other foods and fluids, following which period food is added sparingly and gradually. The loss of weight during the first five days frequently amounts to between six and ten pounds. The amount of fluids added subsequently is never to exceed two, or at the most four, glasses daily. A ten- to twenty-pound reduction is not uncommon within a period of two to three weeks. With this diet we seldom had to resort to mercurial diuretics for the relief of the edema and with the loss of actual body weight and tissue fluids, a marked drop in both systolic and diastolic pressures was very often observed; this was often accompanied by marked improvement in the general condition of the patient. These patients are advised subsequently to have one or two exclusive fruit and vegetable days every week.

Dr. Louis A. Kapp, New York, N. Y.—I should like to ask Dr. Master whether blood sugar determinations were made in the series, and, if so, were there any hypoglycemic conditions observed during the treatment by a low calorie diet. From the investigations by Proger and others we know that some patients if put on a restricted calorie intake react with a lowering of their basal metabolic rates, others do not. The change in the basal metabolic rate in its turn frequently affects the blood sugar levels, blood cholesterol, etc. It, therefore, seems to be of clinical importance to find out whether any significant variations in the blood chemistry data in the individual patients were present in the course of the outlined treatment. While it is generally conceded that a low calorie diet is beneficial to cardiac patients, one would hesitate to go beyond certain limits. It is difficult to comprehend why 800 calorie diets were selected as a standard. I think that age, sex, weight of the patients, as well as the basal metabolic reactions and blood sugar levels, should

*Tr. Am. Therap. Soc. 34: 117, 1934.

have been considered as criteria in determining the appropriate low calorie diets in the cases. What appears to be a low calorie diet for one might be high for another patient.

One more question I would like to ask is whether any deviations from the usual successive changes in the electrocardiogram seen in myocardial infarction were noted in the patients treated with a low calorie diet. For some time I have been engaged in a study on the changes in the electrocardiogram in various blood sugar levels, especially in hypoglycemia. I wonder what experience Dr. Master has possibly had in this respect in connection with the reported method of treatment of coronary thrombosis.

Dr. Meyer Sclar, Brooklyn, N. Y.—I would like to ask Dr. Master how long he keeps these patients on this diet. As soon as the patients begin feeling better, let's say the second week following the acute coronary insult, do they complain of hunger? Also, at the outset he mentioned digitalis and adrenalin are definitely contraindicated. This seems to be universally accepted. However, does he still consider digitalis contraindicated when congestive heart failure sets in, and does he still consider adrenalin contraindicated when the systolic pressure drops to 80 or lower?

While on the subject of drugs—how many cases did he find in which fibrillation began following the coronary insult, and did he use quinidine when fibrillation did set in?

Dr. Simon Fraucht, Brooklyn, N. Y.—I would like to ask how many of these patients were diabetic.

Dr. Arthur M. Master, New York, N. Y.—Naturally we did more than I could report in twelve minutes. We made blood sugar determinations, but there was no change; there was no definite drop below the normal figures. In reply to the question about the diet—of course, we were elastic. There were a few patients who were very hungry. Certainly, we gave them 1,000, 1,100 or 1,200 calories daily. On the other hand, two or three of these very hungry patients, once they experienced the benefit of the diet, refused to go back on their regular diet. We have to this day two or three patients who have remained very thin; they just won't eat. We have not followed the electrocardiograms in great detail although we have taken many. We hope to make some sort of an objective comparison with patients who have had coronary artery thrombosis and had the same regime as ours except that they have had full diets. I think we have the opportunity because Fishberg and his coworkers at the Mount Sinai Hospital recently reported some sixty cases in which they followed the same course except that their patients received the regular diet. They recorded blood pressure readings, circulation times, and other studies that we too have done. Digitalis we do think is contraindicated. We did have patients with congestive heart failure, but it wasn't necessary to give this drug. Patients stand a diuretic like mercurpurine and the acid-producing drugs like ammonium chloride much better. We are afraid, particularly early in the attack, to give digitalis. We did have five patients with transient auricular fibrillation, but they spontaneously returned to a regular sinus rhythm. We never use quinidine in any of our patients. We consider it dangerous in an acute coronary artery thrombosis. I might add, before I close, that the question is constantly put to us whether our work correlates with the work that has been done in Boston. Does this low dietary regime attain the same results that total thyroidectomy does? I do not know. I know this, however: we can over a period of several months keep the basal metabolic readings between minus 20 and minus 35. We think that the mechanism is different from the mechanism that intervenes after total thyroidectomy. In our cases there were never symptoms or signs of myxedema; the blood cholesterol was not increased; and there was no delay in the circulation time.

Department of Reviews and Abstracts

Selected Abstracts

Tennant, Robert: Factors Concerned in the Arrest of Contraction in an Ischemic Myocardial Area, Am. J. Physiol. 113: 677, 1935.

1. Simultaneous registration of optical myograms and aortic pressure pulses indicates that abolition of myocardial contraction similar to that following coronary occlusion is produced in the presence of oxygen by potassium chloride and sodium cyanide, but not by sodium iodacetate.

2. Perfusion of a ventricular zone in the normally beating heart with sodium lactate in buffered blood-Locke's solution similarly arrests contraction. This fact, together with other experimental evidence, is strongly suggestive that excess lactate in itself is a factor in preventing contraction under anoxic conditions although it does not exclude change in pH as another possible mechanism.

Wiggers, Harold C., and Wiggers, Carl J.: The Interpretation of Monophasic Action Potentials from the Mammalian Ventricle Indicated by Changes Following Coronary Occlusion, Am. J. Physiol. 113: 683, 1935.

Monophasic curves, recorded from a dead basal region of the right ventricle and the initially normal apex of the left ventricle, were obtained before and at various intervals following occlusion of the ramus descendens anterior.

In the analysis of such curves, emphasis is placed on two reference points viz., the moment of initial rise, A, and the point of abrupt fall toward isopotentiality on the descending limb, F. Since the interval (A-F) largely determines the area bounded by the curves, it gives more exact information of changes at the exploring electrodes than does the amplitude or contour of curves that can be recorded.

The earliest and most outstanding alteration of direct monophasic leads following coronary occlusion is the reduction in the A-F interval, with consequent decrease in the area bounded by the curve. This reduction occurs without any amplitude diminution about a minute after occlusion and is due to an earlier termination of the potential difference between electrodes. These facts indicate that monophasic potential deviations are not free from potential changes at the initial dead area, but they strongly suggest that the duration and area of the curves are significantly affected by changes under the exploring electrode.

The general deduction is made that variations in the A-F interval or duration of the curve cannot be used as evidence that monophasic curves are due solely to potential changes under an exploring electrode, unless it is shown that the rise and not only the termination changes with reference to deflections of a standard E.C.G.

A second change occurs in monophasic leads from 4 to 5 minutes after occlusion, i.e., 3 to 4 minutes after contractions have been arrested. It consists in a reduction in amplitude, without further abbreviation of the A-F interval and without change in the relation of the rise to QRS complex of an E.C.G. This obviously denotes not only a greater but an earlier development of an oppositely directed potential under the exploring electrode in the ischemic area.

The fact that monophasic curves still appreciable in size can be derived from this area until the ventricles fibrillate is a second bit of evidence that the electrode on the original area of injury exerts an important influence on the curves.

In experiments in which coronary blood flow is restored previous to fibrillation, the monophasic curves revert to their original form. This indicates that the changes described are not those due to dead tissues but to tissue the function of which has been physiologically suspended.

Wolferth, Charles C., and Margolies, Alexander: **The Influence of Varying AS-VS Intervals on Split First Heart Sounds: Its Bearing on the Cause of Split Sounds and the Mechanism of the First Sound,** J. Clin. Investigation **14:** 605, 1935.

1. Two cases are presented, both exhibiting complete heart-block and split first heart sounds. Heart sound tracings showed marked variations in amplitude of vibrations in each component of the split sounds. During certain ranges of P-R relations the variations in the two components appeared to be independent of each other.

2. Evidence previously obtained suggests that in cases with split first heart sounds there is asynchronism in the isometric contraction phase of the two ventricles, corresponding to the split between the two components. This affords a reasonable explanation for the variations in the two sound components, namely, that they are due to different As-Vs intervals on the two sides of the heart. Furthermore, the range of As-Vs intervals associated with increased amplitude of waves differs but little for the two components. Thus, the apparently haphazard variations in the second component are found to be of the same nature as the variations in the first component. Both components behave as do single first sounds when they are influenced by As-Vs intervals which change from beat to beat.

3. In a number of beats recorded, particularly in Case II, the P-wave falls so late with reference to the first sound component that auricular contraction could not have materially influenced this component, although marked increase of amplitude in the waves of the second component occurs.

4. In Case III (in which changes in As-Vs intervals are due to ventricular escape) independent variations in the two components of the first sound occur, which are similar to those observed in Cases I and II. This case is not as favorable for analysis as Cases I and II because the presence of ventricular arrhythmia may also influence the first heart sound.

5. Case IV shows complete heart-block and a prolonged first sound. During a certain range of P-R relations the first part of the sound is represented by vibrations with large amplitude, and during a slightly shorter range the last part of the sound is represented by sounds with large amplitude. Since this behavior corresponds to that of the two components of a split first sound during certain ranges of P-R intervals, it suggests that the prolongation of the first sound is due to slight asynchronism of the two major sound components.

6. All the findings in our cases are in accord with the postulate that one main component of the first sound is contributed by one ventricle and the other main component by the other ventricle. They lend no support to the view that both components arise in a single ventricle and, as a matter of fact, cannot be accounted for on such a basis.

7. It is suggested, on the basis of present knowledge, that major sound vibrations in each ventricle are associated with the period of rapidly rising pressure of that ventricle during the isometric contraction phase and that factors which modify the curve of rising pressure also modify production of sound. The volume of sound does not necessarily parallel the extent of rise of intraventricular pressure; the sounds are capable of varying independently of the output (as shown by optically

recorded arterial pulse waves); it is probable that the gradient of rise of pressure is the most important factor. It has thus far not been determined what structure or structures contribute the main sound vibrations in response to the application of force initiated by the contraction of the ventricular muscle upon the ventricular contents.

Resnik, Harry, Jr., and Friedman, Ben: Studies on the Mechanism of the Increased Oxygen Consumption in Patients With Cardiac Disease, J. Clin. Investigation 14: 551, 1935.

1. The basal metabolic rate is elevated in many persons with congestive cardiac failure and declines as improvement occurs. The degree of elevation (and decline) tends to parallel the severity of congestive failure (and the extent of improvement).

2. The above observations indicate that the increased work of the respiratory muscles associated with cardiac dyspnea adds another load to an already overburdened heart. This factor of respiratory effort assumes greater importance as cardiac failure becomes worse, for the ventilation tends to rise and the vital capacity to fall, thus increasing the ratio, $\frac{\text{Ventilation}}{\text{Vital capacity}}$, in geometric proportions. Procedures which tend to reduce the ventilation (rest, morphine, venesection, paracentesis) are beneficial in part through reduction of the work of breathing.

Flaxman, Nathan: Variability of Murmurs in Mitral Stenosis, Am. J. M. Sc. 190, 396, 1935.

1. The variability of the murmurs in 237 cases of mitral stenosis is reported.

2. Auricular fibrillation was present in 46.6 per cent; it had no effect on the character or type of murmurs audible.

3. Double murmurs were found in 79 per cent.

4. Systolic murmurs alone were present in 15.2 per cent.

5. The murmurs of mitral stenosis were readily recognized by the characteristic rasping sound without resort to isolating the murmurs definitely in the cardiac cycle by timing.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process: The Determination of Antistreptolysin Titer, J. Exper. Med. 62: 129, 1935.

1. A method for determining the antistreptolysin titer is described in detail.

2. The natural human level of antistreptolysin determined in this way is approximately 50 units.

Coburn, A. V., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process: Observations on an Epidemic of Influenza Followed by Hemolytic Streptococcus Infections in a Rheumatic Colony, J. Exper. Med. 62: 137, 1935.

The observations presented in this paper may be summarized as follows:

A study has been made on an isolated group of children with heart disease.

All of these individuals, with one exception, were rheumatic subjects.

Many of them carried a strain of hemolytic streptococcus in the throat flora during the winter of 1934. The organism produced no detectable toxin and was not associated with respiratory disease.

Four patients contracted chickenpox during the winter months. None developed rheumatic recrudescences.

All of the individuals were in good health on March 1.

A severe epidemic of influenza began on March 22. All but six children contracted the disease. The filterable virus responsible for this outbreak was recovered. This agent did not activate the rheumatic process. It was followed by an outbreak of streptococcus infection and appeared to facilitate its spread.

The source of these infections was not traced. They were due to a single type of hemolytic streptococcus which was a strong toxin producer. Its cultural, biochemical, and serological characteristics were different from those of the carrier strain.

Of seventeen individuals proved bacteriologically to be infected with the epidemic strain, fourteen rheumatic subjects developed acute rheumatism; two rheumatic subjects and one patient with congenital heart disease escaped.

These fourteen rheumatic attacks were accompanied by a rise in antistreptolysin titer coincident with the onset of symptoms.

In four of these attacks is was possible to exclude influenza as a causative factor.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process: Observations on the Reactions of a Rheumatic Group to an Epidemic Infection With Hemolytic Streptococcus of a Single Type, J. Exper. Med. 62: 159, 1935.

This study of an isolated colony showed that of seven children who escaped the epidemic streptococcus infection, none developed rheumatic symptoms; and that of seventeen children who contracted the epidemic streptococcus infection, fourteen developed acute rheumatism, and three showed no recognizable rheumatic manifestations.

The seven children who failed to contract infection with *Streptococcus hemolyticus* showed clearly that susceptible individuals may live in close association with an epidemic of acute rheumatism, develop no rise in antistreptolysin titer, and maintain excellent health.

The patient with congenital heart disease demonstrated that a nonrheumatic subject may be infected with a highly effective strain of hemolytic streptococcus, develop a typical antibody response, and yet escape all rheumatic manifestations.

The two patients who, although infected with the epidemic strain, failed to show any antibody response, also failed to develop rheumatic recrudescences.

Environmental, dietary, age, and the other factors investigated did not appear to be significant in this outbreak of acute rheumatism.

Three factors appeared to determine the development of the fourteen recrudescences: (1) infection with a highly effective agent; (2) the disease pattern, peculiar to each rheumatic subject; and (3) the intensity of the immune response of the patient as indicated by the rise in antistreptolysin titer.

Kutumbiah, P.: Rheumatism in Childhood, Indian J. Pediat. 2: 215, 1935.

1. A short summary of the literature on rheumatism in India is given.
2. The contention that there is no rheumatic fever in the tropics is shown to be no longer tenable.
3. Evidence is adduced to show that rheumatic infection in childhood is common in Vizagapatam, a city situated in the tropics.
4. A brief résumé of the salient features of juvenile rheumatism as it occurs in the temperate climates is given.
5. An analysis of fifty cases of juvenile rheumatism from King George Hospital, Vizagapatam, is given.
6. The various phases of cardiac rheumatism are illustrated by typical cases from this series.

7. The age and sex incidence and incidence of polyarthritis, chorea, and nodules are discussed.

8. The frequency of cardiac rheumatism in children suffering from tonsillitis is noted.

9. Few typical radiographs and electrocardiograms of mitral disease are given.

10. It is concluded that rheumatism in childhood is very common in the Vizagapatam district, and in its essential manifestations it closely resembles juvenile rheumatism in the temperate climates.

Bland, Edward F., and Jones, T. D.: Clinical Observations on the Events Preceding the Appearance of Rheumatic Fever, J. Clin. Investigation **14:** 633, 1935.

1. There appears to be no significant clinical difference between the recurrences or recrudescences of rheumatic fever following (1) respiratory infection, (2) other forms of infection, (3) accidents or operative procedures, and (4) a single intravenous injection of typhoid-paratyphoid vaccine sufficient to cause a slight febrile reaction and chill.

2. The probable significance of these observations has been discussed. It is evident that various events precede and apparently influence the appearance of the signs and symptoms of recurrent rheumatic fever.

3. It seems desirable, in view of the observations presented, to consider the rôle of such events as nonspecific until more definite information is available concerning the etiological agent.

Seegal, David, Seegal, E. B. C., and Jost, E. L.: A Comparative Study of the Geographic Distribution of Rheumatic Fever: Scarlet Fever and Acute Glomerulonephritis in North America, Am. J. M. Sc. **190:** 383, 1935.

1. A comparative study has been made of the geographical distribution in North America of acute glomerulonephritis, rheumatic fever, and scarlet fever.

2. The case rate for scarlet fever diminishes progressively from latitude region 50 to 45 degrees to 34 to 29 degrees.

3. The yearly hospital medical admission rate for rheumatic fever in twenty-four hospitals shows a similar decrease in the same latitude regions.

4. In contrast to the diminished case frequency of scarlet fever and rheumatic fever in southern latitudes as compared with northern latitudes, the yearly hospital medical admission rate for acute glomerulonephritis does not vary significantly in the four latitude regions studied.

5. The failure of acute glomerulonephritis to diminish in frequency in southern latitudes might be interpreted as supporting the hypothesis that agents other than the hemolytic streptococcus play the chief etiological rôle in this disease. This does not seem likely, however, since considerable evidence is available incriminating the hemolytic streptococcus as the main incitant of the disease.

6. Since evidence is available ascribing etiological significance to the hemolytic streptococcus in all three diseases studied here, the variation in the geographical distribution of these diseases based upon the limited data presents a problem in specific host and bacterial interaction.

Baker, B. M., Thomas C. B., and Penich, R. M., Jr.: Experimental Carditis: Changes in the Myocardium and Pericardium of Rabbits Sensitized to Streptococci, J. Clin. Investigation **14:** 465, 1935.

1. When a heat-killed culture of beta hemolytic streptococcus is injected intrapericardially into rabbits sensitized to the same organism, an extensive carditis results.

2. The intrapericardial injection of this organism into unsensitized animals produces no such changes.

3. The changes in the hearts of the sensitized animals are characterized by an extensive, nonspecific, inflammatory reaction.

Rafsky, H. A., Bernhard, A., and Rohdenburg, G. L.: Studies in Hypertension: The Production of Experimental Hypertension and a Correlated Effect Upon the Nitrogen Distribution of the Blood Proteins, Am. J. M. Sc. **190:** 187, 1935.

1. Uranium nitrate when injected in small doses into rabbits produces nephritis with hypertension.

2. Cholesterol similarly administered produced a mild hypertension, while in a single experiment cholesterol and lecithin did not.

3. Of the amino acids injected, aspartic acid alone produces definite hypertension. At autopsy the renal lesions of glomerulonephritis were found.

4. The aspartic acid hypertension in rabbits is not dependent upon the presence of the amino or dicarboxylic group.

5. Guanidine carbonate also produces hypertension when injected into rabbits.

6. A marked fibrosis of the spleen was observed in all of the animals which developed hypertension after the injection of aspartic acid.

7. The total, the amide, the hydrolyzable, the basic amino, and the monoamino nitrogen distribution of the whole blood, of the red cells, and of the serum proteins from the same specimen of blood have been determined in seventeen normal rabbits and in six rabbits with hypertension.

8. In rabbits in which hypertension has been produced by the injection of aspartic acid, the basic amino nitrogen fraction of the serum proteins is decreased; the monoamino nitrogen fraction is increased; and there is a rise in the M/B ratio.

Meeker, D. R., Kesten, H. D., and Jobling, J. W.: Effect of Iodine on Cholesterol-Induced Atherosclerosis, Arch. Path. **20:** 337, 1935.

Potassium iodide fed in large doses for from one to three months to rabbits in which atherosclerosis had previously been induced by prolonged feeding of cholesterol does not influence the rate or nature of the involution of the vascular lesions.

Potassium iodide appears to retard the return of the cholesterol content of the blood to normal levels although it markedly depresses the ratio of the amounts of cholesterol esters and free cholesterol. It is suggested that this retardation may be due to mobilization of stored cholesterol from the tissues.

Josephi, Marion G.: Measurements of the Size of the Heart in Normal Children: A Statistical Study, Am. J. Dis. Child. **190:** 929, 1935.

A series of 418 observations on normal children is presented. These observations consist of values for height, weight, age, body surface area, and the usual measurements of the heart.

The measurements of the heart and those of the body have been correlated, and the highest degree of correlation has been shown to exist between the body surface area and the cardiac surface area.

From the relationship of the body surface area to the cardiac surface area, a quotient has been derived which has been found to be a good measure of the series.

Correlation coefficients arranged in order of their degree of relationship are:

(a) Cardiac surface area to body surface area.
(b) Cardiac surface area to weight.
(c) Cardiac surface area to height.
(d) Cardiac surface area to age.

(e) Cardiac transverse diameter to weight.
(f) Cardiac transverse diameter to body surface area.
(g) Cardiac transverse diameter to chest diameter.
(h) Cardiac transverse diameter to height.

The formula of Hodges, Adams, and Gordon for the prediction of the cardiac surface area has been applied to 100 children, and the correlation between the observed cardiac surface area and the predicted cardiac surface area has been found to be poor.

Jones, Edgar: The Demonstration of Collateral Venous Circulation in the Abdominal Wall by Means of Infra-Red Photography, Am. J. M. Sc. **190:** 478, 1935.

Ten cases are presented in which there was evidence or suspicion of hepatic disorders. Clinical findings with regard to evidences for or against associated portal obstruction, as shown by the demonstration of collateral circulation on the abdominal wall, are given. Comparison is made between the clinical findings and those obtained from ordinary and infra-red photographs of the abdomens of the patients presented. These data seem to indicate that infra-red photography may be of value in demonstrating degrees of collateral circulation which are not detected by usual clinical methods. At least it is an excellent means of recording abnormal degrees of superficial venous distention. Suggestions as to further application are made.

Abeles, Milton M., and Schneider, Daniel E.: Electrocardiographic Changes During Encephalography, Am. J. M. Sc. **190:** 673, 1935.

Twenty cases of simultaneous encephalography and electrocardiography are presented with a study of the changes in the cardiac conduction mechanism. The most common changes are those consequent upon stimulation of the pacemaker between the S-A and A-V nodes, transitory nodal rhythm. In one case ventricular extrasystole was observed, and in another auricular fibrillation. In one fatal case, death following encephalography was probably cardiac and followed the excessive injection of air with subsequent bradycardia and collapse at that period when most cases begin to show a return to normal rate. The findings are correlated with other clinical manifestations of vagus stimulation.

Norris, Robert F.: Syphilitic Aortitis in Childhood and Youth, Bull. Johns Hopkins Hosp. 57: 206, 1935.

Two cases of syphilitic aortitis are presented. One was found in a nine-year-old girl and another in a seventeen-year-old boy. There is some evidence that the lesions were of congenital origin. These were the only cases suggestive of congenital syphilis of the aorta among 14,000 autopsies at the Johns Hopkins Hospital. That syphilitic aortitis with involvement of the coronary ostia may be, in rare cases, a cause of sudden death in young people has been emphasized. Gross myocardial necrosis and scarring in cases of syphilitic aortitis resulting from stenosis and atresia of the coronary orifices occur occasionally and should be carefully searched for.

Book Reviews

Das Elektrokardiogramm. Eine vergleichende Studie. By Franz M. Groedel, Dresden and Leipzig, 1934, Theodor Steinkopff.

This treatise consists of two volumes, a volume of text (358 pages) abundantly illustrated with diagrams and an atlas of 200 plates depicting the electrocardiograms discussed. The reproductions contained in the atlas were made by a special process and reach a high standard of quality.

The chief purpose of this work is to present the results of a study of what Groedel is pleased to call "partial electrocardiograms." Using oscillographs coupled to vacuum-tube amplifiers, he recorded simultaneously two standard leads, a standard lead and a chest lead, or two chest leads. Bipolar chest leads in which both electrodes were placed upon the thorax were found to yield essentially the same information as the standard leads. Unipolar chest leads in which one electrode was attached to the right arm and the other was placed upon the precordium proved to be much more useful. It is Groedel's principal thesis that when leads of this kind are employed, it is possible to record separately the right ventricular electrocardiogram and the left ventricular electrocardiogram. To obtain the former, the chest electrode is placed just to the left of the lower end of the sternum; to obtain the latter it is placed in the midaxillary line at the level of the xiphoid process. When these two curves are taken simultaneously with the camera operating at high speed, it may be seen at a glance that in normal subjects the R and T summits of the right-sided curve definitely precede the corresponding peaks of the left-sided curve. The two curves also differ greatly in general outline; in the former R and S are of approximately equal size, and there is no Q; in the latter R is very much larger than S, and a small Q is present. By dividing the height of a given deflection in the one curve by the height of the corresponding deflection in the other, various coefficients are obtained. The first part of the text deals with the form of these two "partial electrocardiograms" in normal subjects, discusses the origin of their various deflections, and presents evidence in support of the view that each of them represents the electrical activities of a single ventricle, or at least closely approaches this ideal.

The second part of the text presents a large number of clinical cases intended to illustrate the abnormalities displayed by the two "partial electrocardiograms" under various circumstances, and to demonstrate advantages over the standard three-lead electrocardiogram which they possess. This part of the book is disappointing. Three to six or more cases, regarded by the author as similar either from the clinical or from the electrocardiographic standpoint, are presented; a few brief notes regarding the history and clinical findings, a very short description of the standard and of the partial electrocardiograms, and the anatomical or functional diagnosis without comment. At the end of the presentation of each group of cases there is a brief summary which lists the different abnormalities shown by the standard and the partial electrocardiograms but usually does very little else. After covering a half dozen different groups of cases, the reader becomes bewildered and must go back and start over.

One group of cases discussed consists of six examples of "circumscribed, left-sided myocardial changes." In each of these the standard electrocardiogram displays abnormalities which have always been considered characteristic of bundle-branch

and Graphic Registration of the Heart Beat is a much more complete and stimulating book, and contains almost everything of value in this field up to 1925. In the German language, Wenckebach and Winterberg's *Die Unregelmässige Herztätigkeit* is also a far more valuable and original work, but appeared as long ago as 1927. Compared with these two books Weber's monograph is briefer than either, has brought the subject up to date (and considerable new work has appeared since 1925 and 1927, respectively), and above all has stressed the physical foundation upon which these instrumental methods of cardiac diagnosis rest. The peculiar value of the book is the detailed description it gives of various types of apparatus and the aid to those practitioners who have no fundamental knowledge whatever of the principles involved in their construction and use. Whether it will ultimately be important for the practitioner to read the details of such instruments as the cathode ray oscillograph, Duchosal's ingenious ink-writing electrocardiograph, and the many types of amplifying electrocardiographs which are described is open to question, but it can do him no harm. The text is profusely illustrated with graphic records; especially noteworthy are the heart sound records; but the technic of these cannot compare with that quite generally seen in this country. The references in Weber's book to scientific and original work by English-speaking authors suffer when compared to those in German. Thus, of 347 references in the bibliography only 36 are to American or British authors. Certainly no one who has lived through the history of this subject would maintain that these figures fairly represent the relative value of the contributions of the two groups. On the whole, however, the monograph presents a straightforward, sound, useful summary of the subject which will naturally be of most value to German readers.

B. S. O.

La Cianosis De Los Cardiacos Negros de Ayerza: Su Estudio Semiologico, Clinico y Fisiopatologico. By Eduardo L. Capdehourat, Jefe de Clinica de la Facultad de Medicina, Buenos Aires, 1934, Aniceto Lopez, 374 pages with 48 illustrations, paper bound.

This study of the "black cardiacs" of Ayerza is a distinct contribution to the knowledge of the pathological physiology and pathogenesis of this obscure and interesting syndrome.

L. A. C.

Klinik und Therapie der Herzkrankheiten. Vorträge für Praktische Ärzte. By Privatdozent Dr. D. Scherf, Assistent der I Medizinischen Universitäts-Klinik in Wien. Vienna, 1935, Julius Springer, 210 pages with 10 illustrations.

Doctor Scherf has provided a manual on the diagnosis and management of heart diseases which is much more important than the unpretentious form of the book would imply. It contains the material of the series of lectures offered by him annually as part of the postgraduate instruction provided by the medical faculty of Vienna.

Certain aspects of this large subject, such as the cardiac arrhythmias, congential heart disease, the acute endocarditides and pericarditis, are not included, but apart from this minor defect, the book deserves unqualified commendation. It is a model of condensed, clear and accurate statement and represents Wiener clinical medicine at its best. The section on "Treatment" shows the discriminating judgment and good sense that is evident throughout the book.

L. A. C.

APPAPEIL CIRCULATOIRE. By Ch. Laubry. Paris, 1935, Masson et Cie. 185 pp.

This work represents one part of the *Collection des initiations médicales* published under the direction of Dr. A. Sézary. It was designed primarily for the student, to serve as an introduction to the study of the circulatory system. In preparing the volume Dr. Laubry has accomplished the difficult task of selecting important points for emphasis, presenting his material clearly and concisely, and avoiding detailed discussions. By careful choice of material, omission of minor points, and condensation of style, he has provided an introduction to the study of cardiology which covers a wide field in a few pages.

E. H.

CONSULTATIONS DE CARDIOLOGIE. By Georges Marchal. (Collection du Médicin Praticien.) Paris, 1935, Masson et Cie. 228 pp.

In this volume we can visit Dr. Marchal's clinic and have presented thirty patients with various types of cardiac disease. The cases have been chosen to illustrate the types of heart disease which are commonly seen as well as several which are unusual: for example, a case of cardiac insufficiency occurring in the course of filariasis. The presentations are excellent with particular emphasis on the physical signs, and following each presentation is a discussion of the diagnosis, treatment, and prognosis. Dr. Marchal lays great emphasis on psychic and emotional factors in the production of symptoms, especially in the case of physicians who have cardiac disorders. He gives his treatment in great detail and is enthusiastic over the value of colloidal sulphur and streptococcus vaccines in rheumatic fever. He makes clear his general plan of management which includes rest, diet, psychotherapy, and drugs, but, while the general plan is clear, his use of drugs often seems arbitrary.

E. H.

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